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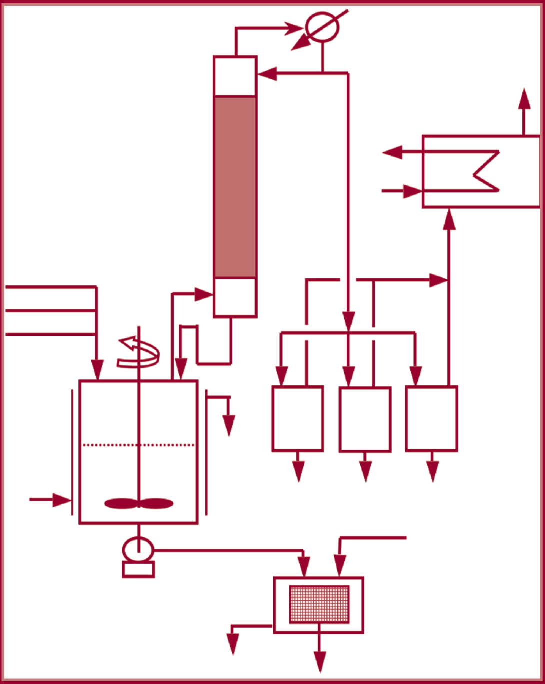
SECOND EDITION

Active Pharmaceutical Ingredients

Development, Manufacturing, and Regulation



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Active Pharmaceutical Ingredients

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SECOND EDITION

Active Pharmaceutical Ingredients

Development, Manufacturing, and Regulation

edited by
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informa
healthcare

New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

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No claim to original U.S. Government works
Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 1-4398-0336-6 (Hardcover)
International Standard Book Number-13: 978-1-4398-0336-3 (Hardcover)

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Library of Congress Cataloging-in-Publication Data

Active pharmaceutical ingredients : development, manufacturing, and regulation / edited by Stanley H. Nusim. — 2nd ed.
p. ; cm. — (Drugs and the pharmaceutical sciences ; 205)
Includes bibliographical references and index.
ISBN-13: 978-1-4398-0336-3 (hb : alk. paper)
ISBN-10: 1-4398-0336-6 (hb : alk. paper) 1. Drug development.
2. Pharmaceutical technology. 3. Drugs—Law and legislation.
4. Pharmaceutical industry. I. Nusim, Stanley. II. Series: Drugs and the pharmaceutical sciences ; v. 205.
[DNLM: 1. Drug Industry—organization & administration. 2. Chemistry, Pharmaceutical. 3. Drug Compounding. 4. Legislation, Drug. 5. Legislation, Pharmacy. W1 DR893B v.205 2009 / QV 736 A188 2009]
RM301.25.A28 2009
615′.19—dc22

2009034997

For Corporate Sales and Reprint Permissions call 212-520-2700 or write to: Sales Department, 52 Vanderbilt Avenue, 7th floor, New York, NY 10017.

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Preface

In the first edition of this book, I spoke of how active pharmaceutical ingredient (API) manufacturing fits within fine chemical manufacturing, describing how enormous changes during the 20th century have occurred in the pharmaceutical industry, causing equally significant changes in the bulk pharmaceutical chemical suppliers.

The intent of this second edition is to not only update what had been written earlier but also to add more definitive information on areas that require further emphasis and to expand the scope of the publication to include areas of significant importance to APIs. We have added a full chapter on biological manufacturing as well as sterile bulk manufacturing that remains a critical part of the field. We have divided the chapter on regulatory requirements into one focusing on requirements and expectations and another focusing on guidelines and strategies.

We have added full chapters on process safety, general plant safety, and environmental control. These chapters reflect the increased importance of handling the more exotic APIs being developed. These three chapters focus on better controlling the environment into which new processes enter and protecting the workers and the population that live near the plant.

In the years since the writing of the first edition, there has been and seems to continue to be a geographical shift for API manufacturing, away from the United States and particularly to India and China and other "third world" sources. This is partly due to the desire of these nations to sell APIs into the European and U.S. market and partly due to the drive for these countries to expand their presence in the world's finished pharmaceutical market itself, which requires API manufacture.

I must point out that each and every topic covered in this volume has changed in some fashion from the past and will continue to change in the future; therefore, the reader is receiving a "starting point" from which he or she must continue to follow the progress of a particular subject in order to keep current.

I wish to express my thanks to Informa for its invitation to assemble the second edition of this book and, particularly, to Sandra Beberman for her advice and continuing encouragement throughout this process.

Stanley H. Nusim

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1 Introduction

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Pharmachemical manufacturing is that branch of the fine chemical manufacturing industry directed to the manufacture of chemicals whose ultimate use will be in a final pharmaceutical dosage form, referred to as the active pharmaceutical ingredient (API). This industry segment has undergone very significant changes in much the same manner, but trailing, the pharmaceutical industry itself, from the time it emerged early in the 20th century.

Thus, we must examine what has happened in the pharmaceutical industry over this period to understand the implications for API manufacturing. This will lead us to the present time and to the goal of this book.

It is our objective to provide a reference book that speaks to those issues that need to be addressed to assure that an existing or proposed pharmachemical operation will meet its objective of supplying an API to meet a medical/market need efficiently and effectively. To better meet this objective, we have added chapters on biological manufacturing and sterile operations, as these operations have grown rapidly to a new level of importance in the API manufacturing environment.

The changes that have occurred are themselves a result of major changes that have taken place both directly and indirectly in and on the industry. These changes include company consolidations, both backward and forward integration; the increased and changed role of quality; the significant intensification of regulatory bodies worldwide; the impact of the greatly increased potency of APIs thereby reducing pharmachemical requirements and the broadening of the market worldwide.

These ideas will be discussed briefly here and touched on in depth in the subsequent chapters.

I. CONSOLIDATION AND INTEGRATION

The "pharmaceutical industry" at the turn of the 20th century was essentially the local pharmacy (or chemist as it was also known outside of the United States). The objective of the pharmachemical supplier to the local industry, at that time, was to provide all of the chemicals, including APIs, as needed by the pharmacist to formulate and compound the prescribing doctor's prescription.

Thus, the great pharmaceutical titans of today, such as Merck, were a fine chemical manufacturer providing a full variety of basic laboratory chemicals and solvents as well as the actives of the day to meet all of the formulating needs of the pharmacist. This activity was common in those early days, as well, to Pfizer, Bayer, and Sterling, among others.

The forward integration of these companies into providing the finished dosage form had by the middle of this past century become the standard rather than the exception as the medical community shifted to writing prescriptions for the local pharmacist to fill, prescribing finished dosage forms rather than the pharmacist compounding his or the doctor's own formulations.

This practice continues to this day, a major factor being the regulatory environment that was created and has grown over this past century. The need to determine the efficacy and safety of those formulated product has grown to very significant proportions during this period.

II. QUALITY

An overriding driving force in this direction, although it may never have been originally intended, has been the shift of governmental control that has been exercised by the U.S. Food and Drug Administration (FDA). A brief discussion of that change is now in order.

The initial purpose of the first Pure Food, Drug, and Cosmetics Act (Act) that was passed by Congress in the first decade of the last century was one of safety. It began by the regulation of those items of commerce that had the potential of poisoning the individual who used it if the product was contaminated. It is for this reason that the Act covered those three specific items, all lumped together although each being used for very different purposes.

The initial focus, at that time, for drugs as well as the other two types of ingested or topically applied products, was lack of contamination as determined by quality sampling and testing. In addition, and extrapolating that issue to new proposed pharmaceuticals, the key data required was the toxicity data and its ratio to the proposed dose level, the "therapeutic index." However, no data or judgment on efficacy was required for its proposed use. Its medical purpose and its ultimate use remained in the hands of the physician and the sponsoring company that promoted it.

In the middle 1950s, this changed dramatically when the Act was amended significantly. The change, driven by congressional hearings and the "thalidomide affair,"[a] now required not only more significant safety data, beyond simple toxicity but also more significantly scientific proof of efficacy. This now placed a new burden on the sponsoring company to provide unequivocal proof, to the government's satisfaction, that the addition of a new chemical entity at the dose level recommended was worthwhile to the public. The shift was due to the recognition that replacing a tried and true medications, which was widely used and its side effects well defined with a new compound with only limited experience in man, was in itself an unknown risk and therefore must be shown to be worth the risk.

This propelled the cost and the risk associated with the discovery and introduction of new chemical entities. This change was absorbed by the industry and set the stage for the next major shift in policy that came in the middle 1970s. This was the establishment of current good manufacturing practices (cGMPs) for the manufacture of pharmaceutical actives as well as the finished pharmaceutical products.

This was the next step in the focus of the FDA on the safety of the product. Up until this point, contamination (or lack thereof) was defined by the presence

---

[a] Thalidomide was an antinausea drug approved in Europe at that time and was before the FDA for approval in the United States. Pregnant women who were normally prone to nausea became an instant market for the new drug. However, very serious birth defects (missing limbs) were experienced in babies borne to many of the women who had taken the drug. This precipitated a worldwide reaction to review the new drug approval process. Needless to say, the drug was not approved in the United States at that time. (In recent years, it has been approved for limited special use in leprosy as well as a cancer treatment.)

(or absence) of foreign impurities not specified in the analytical protocol for the product. This was the case for either the pharmaceutical product or the API that went into the finished product. Although this could be a definitive test for a uniformly distributed contaminant, it would not necessarily find random contamination that occurred in processing or extraneous matter that could enter the system from dirty facilities or poor operating practices.

Finished goods testing, today, as it was at that time always depended upon the assumption of uniformity of product. It was this presumption that permitted the approval and release of a product based on the testing of 100 g of a 100 kg pharmachemical batch or 30 tablets of a lot of 500,000 tablets.

The concept of "cGMPs" and quality assurance became the dominant theme thereby pushing the analytical testing (quality control) into the background.

In principle, one now had to show, to have a product free of contamination, that the manufacturer produced the product in contaminant-free equipment in a clean facility, within equipment designed and tested to show consistent and reproducible product by people thoroughly trained and with full knowledge of the process. Thus, in the United States, this greatly shifted the emphasis to a more rigorous standard of "quality."

The most recent change implemented is the requirement of formal "validation" of facilities, equipment, and the process itself. This is the "proof" that the process and the facility can produce quality product on a consistent basis.

In a similar fashion, one can see the extension of the tighter regulations as they apply in the United States to Western Europe. Through the EU, they have implemented similar standards for the very same reason in Europe; additionally, many of the "third world" nations have already implemented its own GMP initiatives reemphasizing the growing uniformity in such requirements throughout the world.

All these factors are discussed more thoroughly in the appropriate chapters within this book.

III. POTENCY

A subtle change that has emerged in the methods of discovering and developing new drugs in the past decades has had significant impact on the pharmachemical industry.

In the early days, the key to drug discovery often was screening programs where laboratory-screening models were used to test new chemical entities for efficacy against specific disease candidates. Those that were effective, however, often found much of their potency diminished as the active, generally formulated into a pill, was attacked by normal body chemistry as it passed through the digestive system on its way to be absorbed into the blood and transported to the disease site. Thus, only a fraction of the orally ingested drug reached the drug target area. As a result, dose regimens for most oral drugs were 100 to 500 mg.

These dosing levels generated needs for significant quantities of actives in some cases into the millions of kilograms annually (5 billion tablets at 200 mg dose require 1 million kg of active). This resulted is significant dedicated plants for each drug active; particularly since the active was generally a complex organic molecule requiring many chemical steps to synthesize.

However, with the advent of the focus on biochemistry and the new sophistication to understanding the chemistry and biology of the body, today's drugs are designed so as to be more potent. In addition, they can be chemically protected to limit the destruction of the drug as it passes through the body on its way to the target site. Thus, normal dosing of today's "designer" drugs are 5 to 20 mg, 10-fold less than in the past. This reduces the API need for "blockbuster" drugs by an order of magnitude (10 billion tablets at 10 mg dose requires 100,000 kg of API). This also suggests that the lesser volume products would require very small quantities of API making dedicated facilities for them very uneconomical.

These factors have refocused API manufacturing from facilities dedicated to a single API product to multiproduct manufacturing facilities. The added costs of a facility due to the more rigorous cGMPs that now apply favor these kinds of facilities where the cost can be shared by many rather than a single product.

This adds a very critical aspect to the operation because the issues of equipment clean out and turnaround particularly as the issue of cleanliness to assure that cross contamination does not occur.

IV. COMPUTER CONTROL AND AUTOMATION

This industry, like nearly all others, has seen the positive impact of the introduction of computers and automation in the manufacturing facilities. The first impact was in the automatic control systems that are used to maintain accurate and reproducible operating conditions for reaction and isolation systems. This was extended into the integration of multiple operations under computer control often eliminating or at least minimizing people intervention.

This itself caused some concerns for the FDA, which, in the past, depended on manual documentation by operators of batch procedures written and issued by people and people observing and recording all data. This was transformed to computer-recorded data and operating instructions being maintained in computer files. This generated an entire series of new issues that had to be dealt with by both the operation and the FDA. First was security to be sure that the automated instructions are safe from improper and unauthorized changes to the issue of signatures, often electronic signatures, a new concept that has become very common.

V. SUMMARY

The changes referred to above, and the changes that are to occur, without doubt, in the future, drive the need to understand where we are today and where we are going in the future. We have chosen to address the various segments and activities of a pharmachemical plant by having a focused discussion on each in the subsequent chapters.

Again, I repeat a statement from the preface. Each and every topic covered in this volume has changed from the past and will continue to change in the future; therefore, the reader is receiving a "starting point" from which he or she must continue to follow the progress to keep current.

2 Bulk Drugs: The Process Development Task

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I. INTRODUCTION

The purposes of this chapter are few and rather ambitious. The first is to provide a sound perspective of bulk drug process work to the uninitiated and the relatively new practitioner, hopefully without prejudice to the benefit that the approach herein might afford to an experienced but still restless practitioner. All work in a forest that is dense and rich in its variety; it should be regarded from a vantage now and then, and it is from such a deliberately selected vantage that the chapter unfolds.

Then there is the promotion of the power that the purposeful convergence of chemistry, microbiology, and chemical/biochemical engineering can bring to bear on the increasingly difficult task at hand: *the timely conception, development, and reduction to practice at scale of a sound process for the manufacture of a bulk drug*. In the 2000s, timely is shorthand for swift, sound encompasses safety to the environment and to people as well as amenability to various regulatory approvals, and reduction to practice at scale means that the resulting process can be used for reliable manufacture in whatever context might be first required.

> Chemistry, in the context at hand, is the aggregate of synthetic, analytical, and physical chemistry fields within what may be called the drug *process* chemistry discipline at large. The latter, while practiced for decades, has truly come into being in the 1990s, spurred mostly by the greater ascendance of the pharmaceutical industry among chemistry practitioners and by the enhanced role of the bulk drug process in the outcome of drug development. Whereas toxicology or clinical results were the exclusive causes for the demise of drug candidates, the greater difficulty in making today's more complex structures in today's regulatory milieu has for some time raised the profile of their bulk process development task as a factor in the overall outcome (1).
>
> Although first manufacture of the bulk drug is the paramount objective of the technology transfer to manufacturing, the process body of knowledge should be sturdy and complete enough to support expanded manufacture for product growth, as well as provide at least a clear sense of direction for process improvements or second-generation processing.

The above definitions conveniently describe a complex task to which considerable skills need to be applied with due deliberation and under constant managerial attention. Indeed, successful bulk drug process development, as just defined, requires that sufficient interdisciplinary and operational resources be brought together in a cohesive manner, not unlike that required by a critical mass in nuclear fission. Most often, having the resources is not enough, and their cohesiveness makes a significant difference in the degree of success, sometimes making the ultimate difference: *having or not having a new drug available when needed*.

Another sought perspective applies to the integration of the bulk drug process development task with the simultaneous drug development program at large: toxicology, dosage form development, clinical development, and the assembly of the regulatory submissions. The latter, leading to the desired regulatory approvals as the culmination of the overall effort, has in recent years become increasingly dependent on the scope and execution of the process work for the bulk drug, which in some of its aspects has now become fastidious and greatly increased the burdens of the bulk process development task.

As the last objective, the methods of bulk drug process development will be weaved discreetly, if not seamlessly, throughout the chapter: (a) the principal issues that shape the methods, (b) the most trenchant choices confronting the process development team, and (c) some selected heuristics (i.e., empirical rules that, although lacking proof, are useful often enough) distilled from the author's experience.

> As a distinct and credible literature of process development for bulk drugs and fine chemicals has come into being and grows, statements of applicable empirical wisdom are appearing with a modicum of organization (2,3,4,5,6) and the field should one day become amenable to independent study (it is not currently taught formally anywhere). In addition, a journal focused on the field has been published since 1997 as a joint venture of the American Chemical Society and the Royal Chemical Society (7). Alas, the engineering scale-up of synthetic bulk drug processes is still badly understated, as most contributors to the new body of literature are synthetic chemists. For compounds derived from biosynthesis, however, there is a large body of biochemical engineering literature that deals in depth with the scale-up of the biosyntheses and the subsequent "downstream processing" technologies (8,9,10).

The application of the fruits of bulk drug process development to process design, technology transfer and first manufacture will be addressed in the companion chapter 3, as those activities are carried out in a distinct context that overlaps with the R&D activities. Such planes of contact will, of course, be identified in this chapter and their discussion confined to the minimum needed herein.

With regard to the scope of the chapter, it is ambitious in its aim to support the above objectives, yet modest in its depth of descriptive material, since doing justice to the latter would require a much larger volume. Instead, the author has chosen to address the fundamentals along the said objectives, while keeping the descriptive technical material spare and aimed at selected targets of the bulk drug process development task: for example, seeking thermochemical safety, scaling up, achieving the desired physicochemical attributes of the bulk drug, and capturing and applying the process know-how.

As of this writing in 2009, the process development milieu of the bulk drug industry is quite varied—from the large drug company in which all the skills are represented to the small virtual firm that contracts out the work, as well as firms that do selected process development tasks as part of their attempt to secure the eventual manufacturing business from the owner of the drug candidate. The author has not attempted to deal separately with these different environments lest the exposition of the target fundamentals get obscured by the specifics of each case. Instead, the bulk drug process development task is discussed within the continuum of a large drug company, and commentary that applies to other contexts has been inserted, hopefully in a sparing and incisive manner.

The reader should be alerted to an additional choice of the author. Although the increased regulatory expectations have deeply transformed the process development task, the paramount stance for the practitioner remains intact: *know and understand your process, reduce it to practice soundly, and operate it in a disciplined manner*. Accordingly, this and its companion chapter, aimed at the fundamentals, avoid the spectrum of the current good manufacturing practices (cGMPs) subject, which seems to have soaked so much of the energy of process practitioners throughout the bulk drug industry. However, the issues associated with the assembly of regulatory submissions [New Drug Application (NDA) and the like] and with the expectations of the subsequent approval process will be discussed as required to meet the objectives of the chapters.

Finally, the diligent reader of these two chapters, armed with the perspectives provided herein, should find that continued study of the literature can be quite fruitful. To assist in that task, a selection of references is included, most of which are cited throughout the text, with the rest cited separately as suitable reading for the studious.

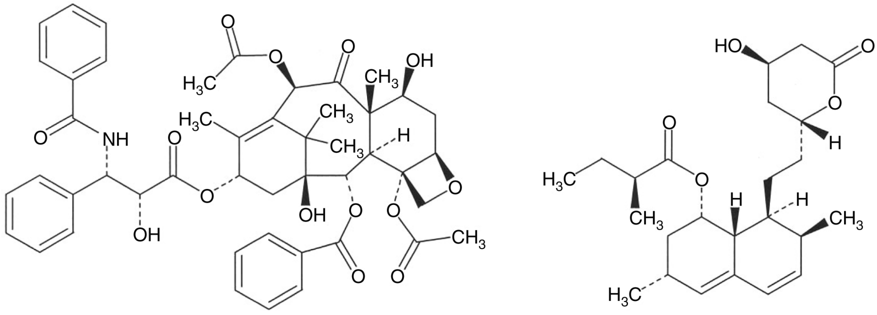
II. THE BULK DRUG PROCESS AS PART OF THE DRUG DEVELOPMENT PROGRAM

A. The Chemical Process of a Bulk Drug

In the context of this chapter, a *bulk drug* or a *bulk drug substance* is a material—a single chemical compound with the desired biological activity—obtained in bulk form and destined for the preparation of dosage forms. The latter, when administered in a prescribed manner to the target patient, animal or plant, delivers the drug so as to elicit a desired physiological response and, in due course, the intended therapeutic or protective result. More recently, terms such as *active pharmaceutical ingredient (API)* or *bulk pharmaceutical chemical (BPC)* seem to have overtaken the usage, seemingly as the result of their adoption by regulators in the United States. Herein we will use the original term *bulk drug* (or *bulk*), as it most aptly describes the material—a drug that is obtained and characterized in bulk form. However, we will confine our scope to those compounds commonly known as *chemical entities*—drugs of relatively small molecular weight that can be characterized well by current methods of chemical and physicochemical analysis. In doing so we are excluding those macromolecules, substances, and preparations of biosynthetic origin that are collectively known as *biologicals*. The processing methods used in biologicals, albeit based on the same fundamentals, are significantly different from those applied to chemical entities, and their process development, registration and manufacture also take place in a rather different environment. In addition, organic compounds categorized as nutritionals and fine chemicals at large are not within this scope, their processing similarities with bulk drugs notwithstanding.

Bulk drugs are obtained through three chemical processing routes:

a. Extraction, recovery, and purification of the drug from biomasses of natural origin or from fermentation (Fig. 1): (*i*) paclitaxel is extracted from various *Taxus* plants, and (*ii*) lovastatin is biosynthesized in the fermentation of nutrients by *Aspergillus terreus*.
b. Semisynthesis, in which a precursor compound from a natural source or fermentation is converted to the target drug by synthetic chemical modification:



Paclitaxel – Found in *Taxus* plants.

Lovastatin – From certain microbial cultures.

FIGURE 1 Bulk drugs from natural sources: Paclitaxel (antileukemic and antitumor) and lovastatin (inhibitor of cholesterol biosynthesis) are examples of the diverse and complex structures made by plant and microbial cell biosyntheses, respectively. In most instances of such compounds having desirable biological activities, their structural and chiral complexities make chemical synthesis not competitive with isolation from biosynthesis.

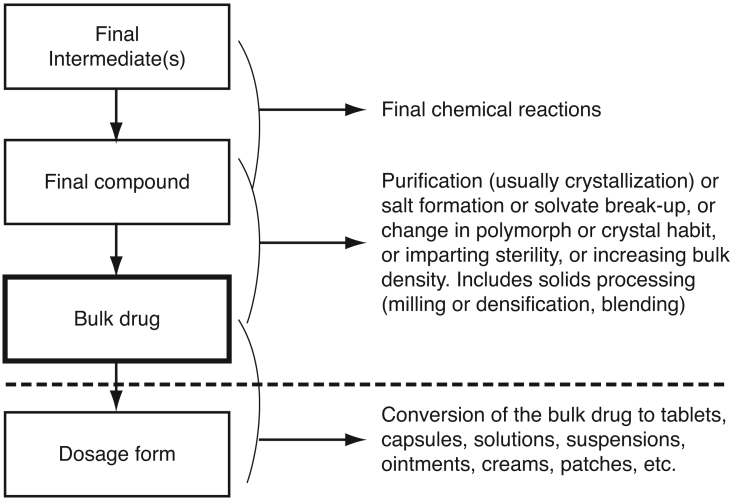

Final Intermediate(s)
Final compound
Bulk drug
Dosage form
Final chemical reactions
Purification (usually crystallization) or salt formation or solvate break-up, or change in polymorph or crystal habit, or imparting sterility, or increasing bulk density. Includes solids processing (milling or densification, blending)
Conversion of the bulk drug to tablets, capsules, solutions, suspensions, ointments, creams, patches, etc.

FIGURE 2 Semisynthetic bulk drugs: ampicillin (antibacterial) from penicillin G. Modifications of biosynthetic structures are often created to improve the in vivo attributes of the original compound, utilizing the biosynthesis product as the starting material containing most, if not all, of the structural complexity that provides the basic biological activity. Similarly, codeine (analgesic), although found in opium from *Papaver* plants, is most economically made by methylation of morphine, which is more efficiently isolated from opium.

(*i*) Penicillin G (from fermentation) is converted to 6-aminopenicillanic acid, which in turn is reacted with an acyl chloride to afford ampicillin, and (*ii*) natural morphine is methylated to codeine (Fig. 2). Both routes to bulk drugs take advantage of the diversity and richness of molecular structures found in natural sources, where many important biological activities are found.

c. Total synthesis from simple starting materials or less simple intermediate compounds (Fig. 3): (A) fosfomycin from commodity chemicals and (B) lobetalol from 5-bromoacetyl salicylamide.

> In either total synthesis or semisynthesis processing, sometimes a desired synthetic transformation is best done by an enzyme. Such synthesis step, whether using a preparation of the enzyme or the host microorganism, will be considered a chemical synthesis step (a *biotransformation* or a *biocatalytic step*) and not a fermentation for biosynthesis.

Whichever of these routes is used to obtain a bulk drug constitutes the *chemical process*. Further processing of the bulk drug to obtain the dosage form constitutes the *pharmaceutical process*. This distinction is depicted in Figure 4, where simple graphical means are used in an attempt to differentiate the *bulk* character of the product of the chemical process from the *discrete* character of the product of the pharmaceutical (or *dosage form* or *secondary manufacturing*) process. The distinction also reflects their very different technology, manufacturing, and regulatory environments.

> In the current pharmaceutical parlance, the term *API* (for *active pharmaceutical ingredient*) is used most often as descriptive of the biological activity contribution.

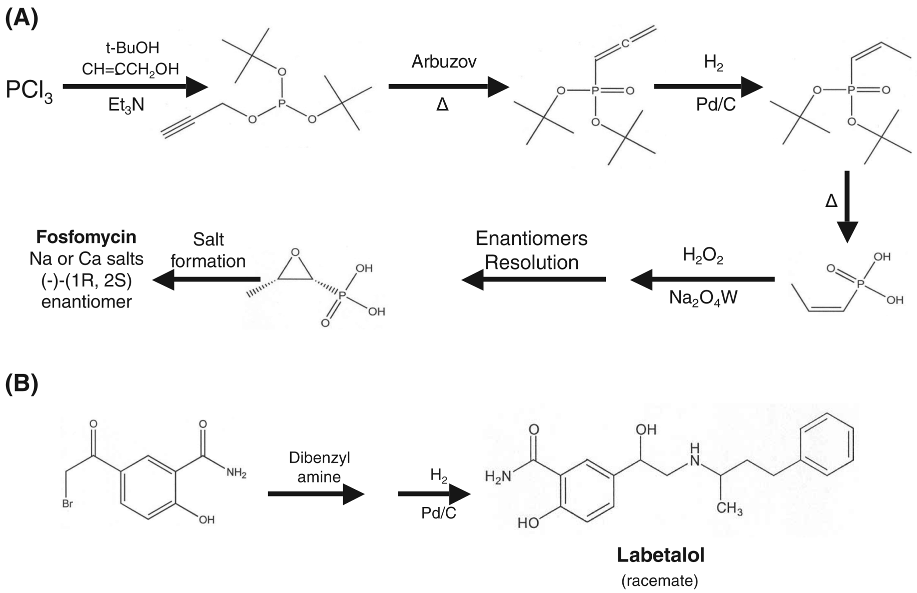


FIGURE 3 Drugs by total synthesis: Fosfomycin (antibacterial) is a good example of the manufacture of a bulk drug by total synthesis from basic chemicals, albeit the compound is of biosynthesis origin. Alternatively, and more frequently, the manufacturing process is simplified by tapping on commercially available compounds of greater structural complexity (*intermediates*), such as 5-bromoacetyl salicylamide as the starting material for lobetalol (antihypertensive). Even if the intermediate is custom made by others, the process development and manufacturing task for the drug developer is greatly simplified relative to the use of basic or building block chemicals.

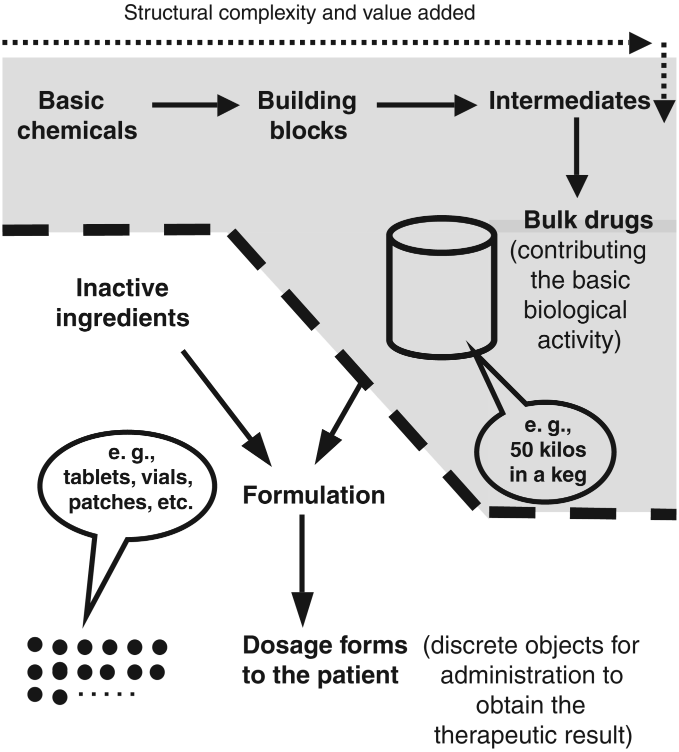

Structural complexity and value added
Basic chemicals
Building blocks
Intermediates
Bulk drugs (contributing the basic biological activity)
e. g., 50 kilos in a keg
Inactive ingredients
Formulation
e. g., tablets, vials, patches, etc.
Dosage forms to the patient
(discrete objects for administration to obtain the therapeutic result)

FIGURE 4 The domains of chemical (bulk drug) and pharmaceutical (dosage form) processing, with the chemical processing domain defined by the shaded area of the diagram.

Herein, however, the term *bulk drug* is used instead as descriptive of the physical and chemical character of the subject material, with its biological activity taken as obvious. Indeed, the conventional term for the other ingredients added to formulate the dosage form is still *inactive pharmaceutical ingredients*.

As we proceed, unavoidably some other terms will be used that may not be familiar to all readers. Accordingly, an effort will be made to define such terms at the point of first use, as well as to use them sparsely. For example, *unit operations* are those methods that can be found repeatedly used in chemical processing and that have a common phenomena root, their many variations notwithstanding—filtration to separate solids from an accompanying liquid, distillation to separate volatile components from a mixture, or milling to reduce the particle size of particulate solids. The organization of chemical processing on the basis of such unit operations was crucial to the development of organic chemical technology, which was originally arranged on the chemistry basis of *unit processes*, such as nitration, sulfonation, or esterification. Whereas the latter organized knowledge on a strictly descriptive basis, the unit operations approach made possible the study of processing phenomena on the basis of generalized principles from physics, chemistry, kinetics, and thermodynamics, which could then be used to undergird methods applicable in the context of any chemical process and over a wide range of scale and circumstances—hence the keystone role that unit operations played in the advent of chemical engineering as a discipline, with a practice quite distinct from that of the earlier industrial chemistry.

B. A Perspective

Process development of a bulk drug consists of three distinct tasks:

a. Preparation of the bulk drug, as needed, by the overall development effort—*the preparative task*. The scope of this task varies over a wide range, as shown in Table 1.
b. Definition and achievement of the desired physicochemical attributes of the bulk drug, as needed, by the dosage form development—*the bulk drug definition task*.
c. Acquisition and organization of a body of knowledge that describes a sound process for regulatory submissions and technology transfer to first manufacture at scale—*the body of knowledge task*.

TABLE 1 Bulk Drug Demands of the Various Drug Development Phases

Preclinical phase—initial toxicology, probes on drug bioavailability, data gathering for the IND, additional animal studies, etc.	Supplies to be delivered over 2–6 mo.	Total ~5–50 kg.
Phase I—use in humans (20–80 mostly healthy subjects) for pharmacokinetic, pharmacological, routes of administration, dose-ranging and tolerance studies. Continuing toxicology and dosage form development. All aimed at the design of phase II/III studies and defining the target dosage forms.	Supplies to be delivered over 6–12 mo.	Total ~20–100 kg.
Phase II/III—increasingly large number of patients (up to thousands) in studies for therapeutic effectiveness (initial and confirmatory), dose and regimen determination, evaluation of target populations for safety and efficacy, support of desired claims, market specific and dosage form specific studies, etc. Continuing toxicology and dosage form development, stability studies. All aimed at the assembly of the dossier.	Supplies to be delivered over 18–48 mo.	Total ~300 to >2000 kg.
Phase IV—post-approval studies for optimization of drug use, pharmacoeconomic data, morbidity and mortality data, head-to-head and concomitant drug uses, etc.	These studies are generally supplied from bulk drug made in the manufacturing operation.	

Notes:

1. The IND (Investigational New Drug) is the submission requesting the USFDA's exemption from drug shipping in interstate commerce, thus signaling the intent to initiate study in humans (or target species if a veterinary drug). Dossier is a term often used to describe the total body of knowledge on the drug candidate, from which individual submissions are assembled for filing with the various agencies, for example, the New Drug Application (NDA) to the USFDA.
2. The range of bulk drug totals reflects the wide differences among drug candidates and their programs. Issues such as drug potency and dosage regimens, low animal toxicity, length of treatment to the clinical endpoint, relative difficulty of dosage form development, number of dosage forms developed, and scope of the clinical studies are the principal factors determining the demands for bulk drug. Obviously, relatively infrequent extremes exist on both ends: from a low end for drugs such as dizocilpine, paclitaxel, and some experimental oligonucleotides to a high end for HIV protease inhibitors (high doses) and some cardiovascular drugs (clinical studies of very large scope).

Abbreviation: USFDA, United States Food and Drug Administration.

Source: Author's observations from involvement in numerous drug development programs.

However, these tasks cannot be directed to successful and timely completion unless viewed and managed as a veritable trinity, their differing demands and instantaneous urgencies notwithstanding. Drug development is a fast paced and difficult enterprise; it presents frequent junctures at which the need to focus on the most compelling task needs to be artfully balanced with other needs lest the aggregate task be compromised—all three tasks need to be completed at the same time for timely and successful product launch. Selected instances of such balancing, in which some risk is often inevitable, are discussed throughout the rest of the chapter; therein lies the crucial need for overall coordination of *each* drug's development program.

> Although various models exist, today's drug development is generally facilitated by a coordination mechanism and forum, usually in the form of a cross-functional team that drives and manages a drug candidate. The principal objectives are to have and execute: (a) a drug development plan, (b) rigorous means to closely track its execution, and (c) mechanisms to effectively respond to events and findings that invariably arise in spite of the plan. Indeed, the development of a new drug encompasses a myriad activities and objectives that are extremely cross-linked among the various disciplines contributing to the effort. Clearly, the bulk process development team needs to be well represented in the cross-functional forum throughout the drug development cycle.
>
> Success in development coordination means that, no matter which coordination model is used, there must be prompt and effective resolution of most issues and difficulties, say >90%, *at the team level*, with the rest going up to a broader and more senior team of the R&D organization (i.e., the heads of the disciplines, functions, and those above). Indeed, the direction and operation of such teams have become a distinct function (it will be referred herein as *drug coordination*) with its own set of skills and not unlike the distinct set of skills in new drug submissions and approval—the *regulatory affairs* function.

The relationships of the three basic tasks with the overall drug development program are depicted in Figure 5 in rather simple terms, whereas the specifics of each relationship will be discussed under the heading of each task. The arrows indicate the flow of materials from the preparative task and the flow of information and know-how from each task to the others and to the drug development at large.

It is also useful to depict the bulk drug process development cycle on a Cartesian coordinate plane (Fig. 6). The abscissa axis represents progress since the onset of development of a compound, and although progress along well-defined milestones is used, one might also look at the abscissa as measuring the applied technical effort or, less precisely, the extent to which the bulk drug process has been reduced to practice (e.g., kilos of bulk drug made, batches made, or versions of the process piloted). Inevitably, the abscissa scale shown herein is arbitrary, albeit deliberately selected; the experienced reader will probably readily think of an example with a more apt progress scale—thus the need to deal with the latter in terms of more distinct *stages*, which Figure 6 attempts to depict.

> Were elapsed time to be used, the distance between *phase II/III* start and the *dossier* filing milestones would be quite variable from drug to drug, as that interval depends on the scope of the clinical program and on the therapeutic target. Whereas osteoporosis, diabetes, and depression require considerable time to reach their efficacy endpoints, those for bacterial infection or pain relief, for example,

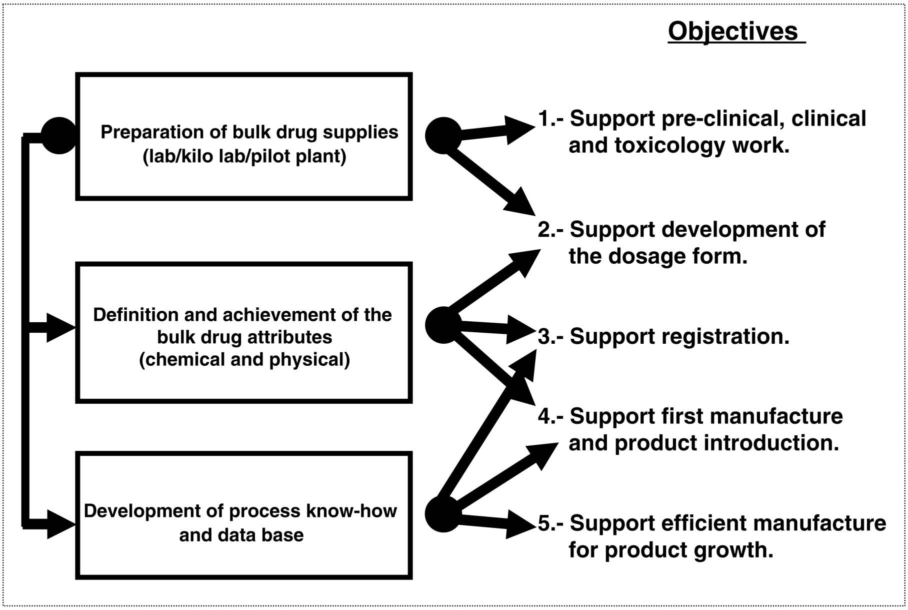

Objectives
Preparation of bulk drug supplies (lab/kilo lab/pilot plant)
Definition and achievement of the bulk drug attributes (chemical and physical)
Development of process know-how and data base
1.- Support pre-clinical, clinical and toxicology work.
2.- Support development of the dosage form.
3.- Support registration.
4.- Support first manufacture and product introduction.
5.- Support efficient manufacture for product growth.

FIGURE 5 The three basic tasks of bulk drug process development. These tasks exit concurrently throughout most of the development cycle, albeit their burdens vary through the cycle. Nevertheless, managing well all three tasks as inseparable parts of a single overall endeavor is the principal managerial challenge in bulk drug process development.

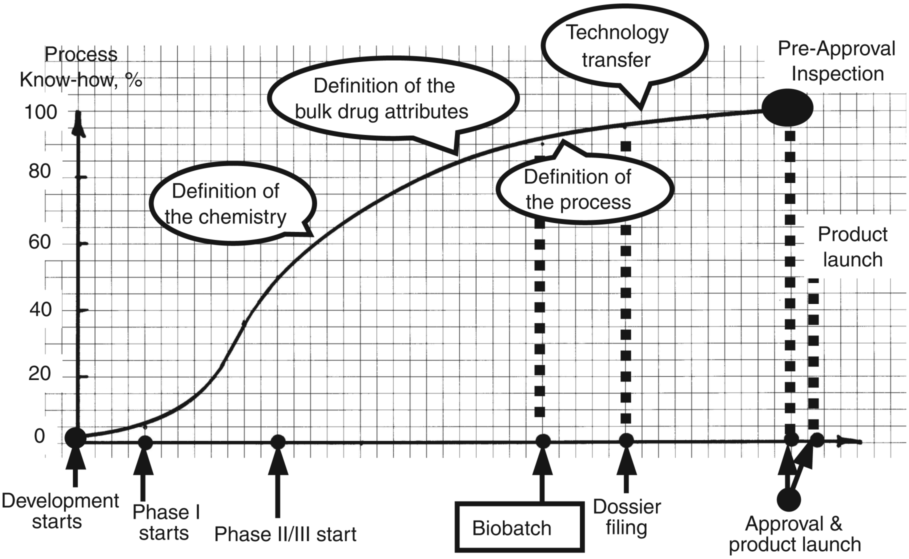


FIGURE 6 The process know-how versus applied effort plane, including the major milestones of bulk drug process development. As defined herein, 100% know-how describes the body of knowledge needed for registration and reliable first manufacture for product launch, whereas additional know-how accumulates with manufacturing experience and follow-up work that might be done for process improvements or a second generation process.

arrive much sooner. For this, and for other reasons related to the intended scope of the drug development (e.g., claims structure, schedule of filings, and multiple routes of administration), the elapsed time scale is unsuitable for the *process* know-how purposes of Figure 6. Instead, applied effort or extent of reduction to practice of the process relate directly, if not strictly in direct proportion, to the acquisition of the process know-how.

Although the *biobatch* and *preapproval inspection* prerequisites are specific to United States Food and Drug Administration (USFDA) approvals, analogous expectations are arising in other drug agencies in the major markets (more on this in chapter 3). The *biobatch* is a distinct marker in dosage form development in that it serves as the bioavailability/bioequivalence bridge to pivotal clinical studies as well as the bioavailability/bioequivalence reference for all subsequent dosage form output. As such, the biobatch reflects the process that goes into the dossier, *uses representative bulk drug* and excipients, and its size is no less than 10% of the intended manufacturing scale. *Preapproval inspection* is a methodology employed by the USFDA to ascertain, at its discretion, that the intended manufacture of dosage form and bulk drug corresponds to the processes used in the pivotal clinical studies and described in the NDA or other new drug submissions.

The ordinate axis, on the other hand, is straightforward, as it measures the fractional bulk process know-how relative to that required for regulatory approvals and for sound first manufacture. Note, therefore, that it is not being suggested that at 100% on the ordinate axis there is nothing else to be learned about the process; instead, *the 100% ordinate value merely describes the knowledge required to fulfill the said process development objectives*. Indeed, further gains in process know-how are always realized with manufacturing experience, and mature processes often differ appreciably from their first manufacture versions, by virtue of gradual improvement or from significant step changes (*second-generation processes*), although most often the seeds for such later developments are planted in the original development body of knowledge. Thus, the curve in Figure 6 describes the accumulation of know-how during four distinct phases of the process development effort:

a. The *preparative stage*, during which the effort is focused on making available kilogram amounts of the bulk drug to the preclinical, toxicology, and phase I work, usually not based on the eventual synthesis route, let alone the eventual process.

   Whereas the synthesis *route* (or *scheme*) describes the intermediate chemical structures sought to arrive at the final compound (starting materials, synthesis approach, and probable chemical reactions to use), the *process* describes how the route is implemented at a much higher level of detail (solvents, catalysts, purifications, isolations vs. straight-through, etc.).

b. The *development stage*, in which the preparative work is scaled up and the synthesis effort goes into high gear, aimed at the manufacturing route *and* process. It is in this stage that the chemical engineering effort is applied in earnest, first to support the scaled-up preparative work and then to address the scale-up issues of the manufacturing route.

   Ideally, the chemical engineering contribution starts early so as to appropriately influence the seminal choices being made by the process chemists as to route. This influence is reasonably apparent with respect to issues of thermochemical safety and probable environmental impact; yet, there is across-the-board synergy that a chemistry/engineering dialogue can exploit. The latter is particularly true in those instances when the chemists perceive a desirable approach as not being feasible on grounds of scale-up difficulty or, more simply, because of lack of experience with some demanding processing conditions.

c. The *consolidation stage*, in which the synthesis route is fully settled and the specific process for it is defined at the level of detail that permits process design for the manufacturing plant, definition of the bulk drug attributes, and the assembly of the dossier. Also during this phase all the preliminaries for technology transfer are carried out and the stage set for first manufacture.
d. The *technology transfer stage*, in which the process is run in its first manufacturing venue, its performance established, and the bulk drug needed for product launch produced. Also during this phase the manufacturing scheme receives approval within the approval of the dossier, often after plant inspection by the approving agencies.

From the preceding definitions, a discussion of the specifics of each stage is now possible, also based on the depiction of the bulk drug process development cycle on the know-how versus the applied effort plane introduced in Figure 6. During these stage-specific discussions, the three bulk development tasks will serve as the basis and along the lines of Figure 5.

C. The Stages of Bulk Drug Process Development

1. The Preparative Stage

Although preparative work takes place throughout the process development cycle, this first stage is most aptly described as the *preparative stage*. Its focus, although not exclusively, is the preparation of limited amounts of bulk drug for assorted preclinical purposes and then is followed by first scale-up to support phase I activities, which include testing the drug in healthy subjects (humans or target animals if a veterinary drug).

Starting with bench scale equipment (up to 100 L in the so-called *kilo lab*) or pilot scale fermentors (up to 5000 L when titer is low), this early preparative work uses whatever synthetic method or fermentation conditions (the microorganism and the nutrients) are immediately available. In most cases of synthesis, the route may be a somewhat streamlined version of the discovery route or a temporary route that may or may not include parts of synthesis schemes being considered for eventual development. In most cases of biosynthesis, the microorganism is that from the discovery stage but taken from whatever stage of microbial strain improvement is amenable to scale-up from shake flasks or bench scale fermentors.

Fermentation processes at this stage are generally of very low productivity (final concentrations of the target compound of <1 g/L), making access to relatively large fermentors most helpful, including, in cases of dire need, the use of manufacturing scale units (up to 75,000 L), the poor scaled-up performance of the early stage notwithstanding. The analogy for chemical synthesis is the arduous operation of lengthy procedures in the kilo lab, the low yields notwithstanding.

Although the kilo lab will be described more fully later on, it may be said at this point that the kilo lab is a larger-scale lab, traditionally used for running preparative procedures rather than experimentation.

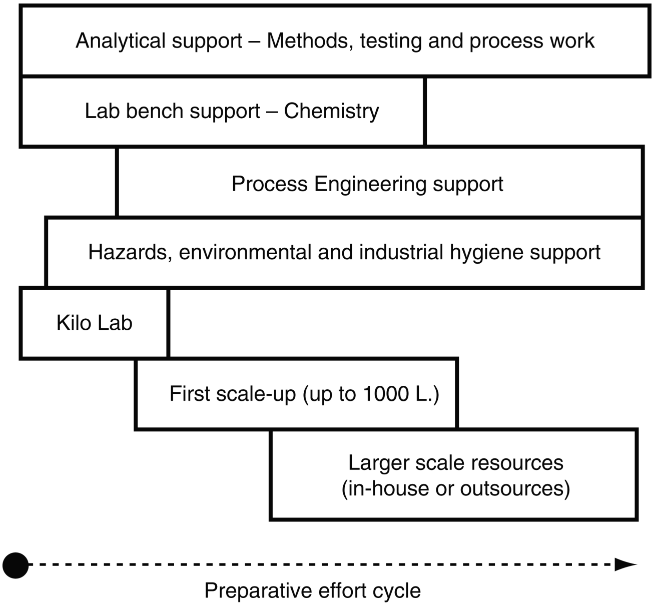

Analytical support – Methods, testing and process work
Lab bench support – Chemistry
Process Engineering support
Hazards, environmental and industrial hygiene support
Kilo Lab
First scale-up (up to 1000 L.)
Larger scale resources
(in-house or outsources)
Preparative effort cycle

FIGURE 7 The resources for the preparative task. The need to engage larger-scale resources depends on the scope of the preparative task, which can vary widely (Table 1 and Fig. 8).

Preclinical and phase I development work is crucial in that it determines the merit of further development or, hopefully, the adjustments that need to be made to move the compound forward—thus the importance of providing the required material on time to get those answers as soon as possible. This reflects on the need for capital investment in facilities such as the kilo lab or pilot plant, and we will discuss elsewhere in this chapter the challenges of this stage of development when the preparative stage depends on *outsourcing* (the reliance on outside suppliers). Indeed, sufficient internal resources for the *preparative stage* is a clear competitive advantage, with the optimal setting providing the means—hardware and engineering skills—to swiftly overlap the kilo lab work with pilot plant work up to, say, 1000 L vessels and the appropriate auxiliaries and operating environment [safety, industrial hygiene (IH), and pollution abatement]. Figure 7 depicts this preparative environment, whereas Figure 8 complements the range of preparative scopes presented in Table 1.

Also depending on the resources of the organization, synthesis bench work may take place in search of routes that can support a manufacturing process, as the routes used during the discovery phase are largely unsuitable on the basis of projected cost, length of the synthesis cycle, commercial unavailability of starting materials, or their perceived inferiority relative to what the process chemists foresee as attractive alternatives. Clearly, the compelling wisdom of such early synthesis work needs to be balanced against the resources available and, most of all, against the empirical probability of less than 20% that a drug candidate at that stage will reach the market, as indicated by Table 2.

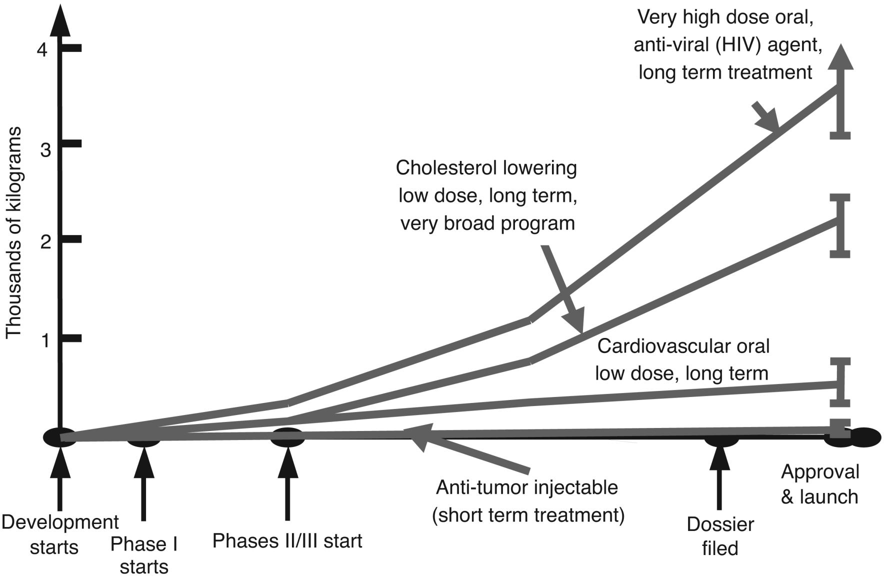


FIGURE 8 The scope of the preparative task. Some examples to illustrate the dependence of the preparative effort on drug potency, therapeutic target, and scope of the clinical effort.

TABLE 2 Best Practices Probabilities of a Drug Candidate Reaching the Market

Drug candidates in the preclinical phase	5–10%
In phase I	10–20%
In phase II	30–60%
In phase III	60–80%
Post–NDA filing	>95%

Notes:

"Best practices" refer to drug development organizations with established good records of bringing drugs to market. In particular, best practices include a high hurdle for a drug candidate to enter development or phase I.

Source: Author's assessment from assorted estimates, including those from the PhRMA Annual Report—online edition, 1997. While the figures from total compounds synthesized (or total number of biologically active compounds) have increased as the methods for generating actives improve their total output, the above figures *after entry into development* have remained largely unchanged. The above ranges probably reflect the adequacy of the tools used to assess the merit of developing an active compound and the rigor of the criteria for moving a compound forward. More recently (2005–2009), the above probabilities for drug candidates in Phase III have decreased significantly.

Whereas medicinal chemists practice organic synthesis as an indispensable tool and are largely oriented upstream (toward the domain of biological and pharmaceutical attributes of the compounds they work with), process chemists in the drug industry practice synthetic chemistry as their profession and are oriented downstream (toward the reduction to practice beyond their lab bench)—thus the usual discontinuity in synthetic route at the discovery/development boundary.

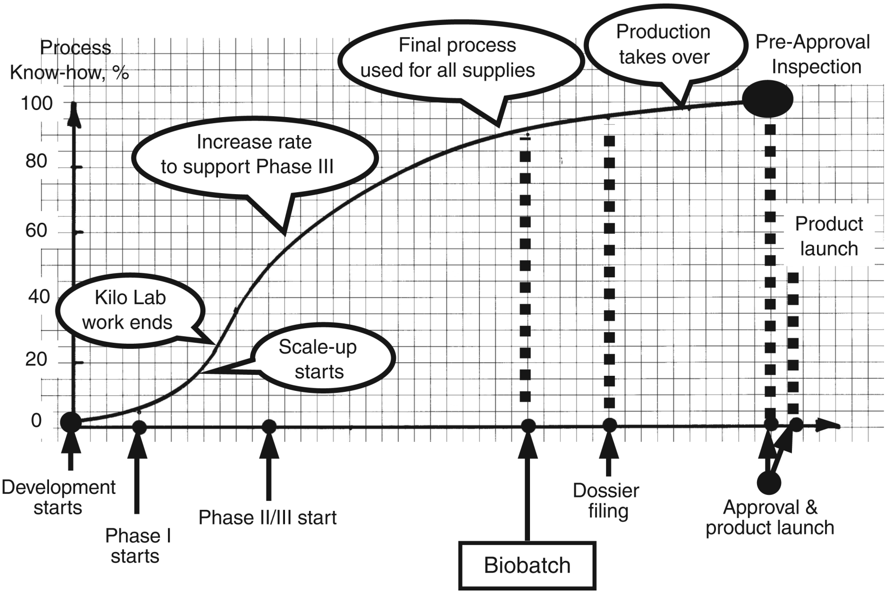


FIGURE 9 The preparative effort in the know-how versus applied effort plane. The principal preparative milestones are shown.

Although sometimes much is made about smoothing and simplifying the discovery synthetic route (eliminating isolations and purifications, shortening the processing cycle and using less expensive materials), the most desirable contribution of the process chemist is the conception of a distinctly advantageous synthesis route that can then be developed and engineered into a sound manufacturing process. Such a route would bring the advantages of fewer steps from reasonably available starting materials, environmental benevolence (or, preferably, *green chemistry*), parallel moieties that can converge into shorter synthesis cycles, stereoselectivity, and similarly decisive gains.

As a summary, Figure 9 focuses on the *preparative stage* and the rest of the preparative effort on the know-how versus applied effort plane, whereas Figure 10 depicts the materials flow from the bulk drug preparative effort at large.

2. The Development Stage

As made clear by the slope of the curve in the know-how versus applied effort plane (Fig. 6), the *development stage* comprises the most productive development effort:

a. Synthesis work at the bench scale seeks the eventual manufacturing route in earnest, preferably on more than one approach, with all promising a substantial, if not overwhelming, advantage over the current preparative procedures.

   In chemical synthesis, the route is basically driven by the structure of the target compound. Within that logic, however, the creativity of the process chemist is bounded only by the realities of starting materials availability.

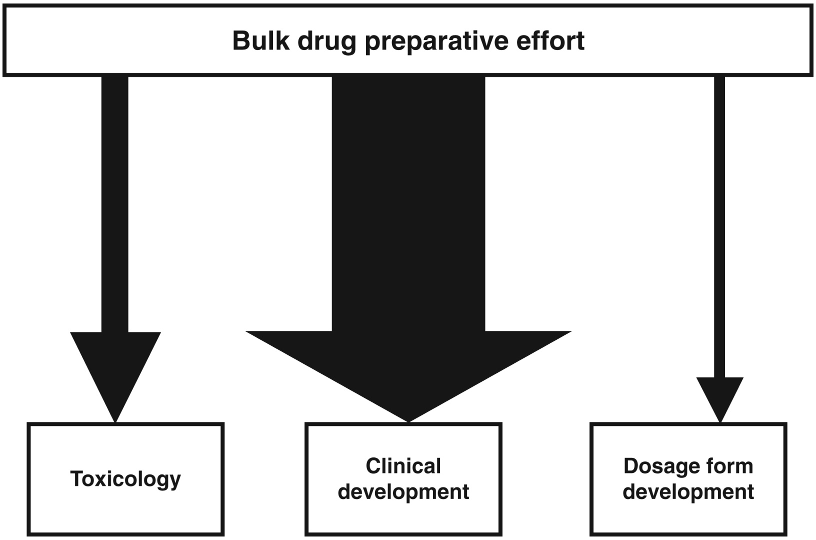


FIGURE 10 Materials flow from the bulk drug preparative effort. The width of the arrows *approximately* indicates the relative amounts of bulk drug going to the users in the overall drug development program. Examination of this figure and Figure 9 provides an equally approximate description of the bulk drug usage as a function of the development cycle.

However, examples of bulk drugs made from commodity chemicals are now few and rapidly disappearing (thiabendazole and l-methyldopa, for example), as the more complex structures of today's medicinal chemistry preclude synthesis from basic raw materials. Instead, today's process chemist must be very alert to what the fine chemicals industry offers (or could be induced to offer) by way of suitable building blocks or intermediates and the corresponding manufacturing capabilities. Such alertness, combined with creative synthesis skills, is the key to truly advantageous routes. This theme is discussed amply and in depth in some of the previous references (2,3,4,5), as well as in Saunders's compendium of selected major drugs (11). In the extreme, the total synthesis of structurally rich natural products, although rarely aimed at a manufacturing process, offers leads and inspiration to the process chemist, as well as blazes the trail with new reactions, some of which are eventually used in bulk drug syntheses (12).

In celebrating the opportunities for the creative process chemist we should not neglect factors such as the increasing desire for environmentally benevolent chemistry (*green chemistry*) or the prevailing business model in the bulk drug industry, by which the range and scope of chemical processing has been narrowed in favor of contracting out (*outsourcing*). There is also, on management's part, the reluctance to practice hazardous chemistry (nitration, sulfonation, phosgenation, etc.), with that spectrum of processing now all but ceded to contract manufacturers.

Some compounds of natural origin products have been manufactured by total synthesis when structurally simple (e.g., chloroamphenicol, fosfomycin) or when inevitable to bring a significant drug to market, as in the case of imipenem (13).

The selection of the chemical route, which is invariably made before it has been sufficiently reduced to practice, is the strategic decision, as it has the greatest potential to define the process and its overall performance—costs, reliability, environmental impact, etc. Accordingly, it is a decision that is best made with the benefit of sufficient engineering assessment, as sometimes the chemical appeal is not sufficient. Indeed, engineering assessments of capital and operating costs, environmental impact, and issues of process design and scale-up bring sharply into focus the general direction as well as the specific development actions that the route requires to become the manufacturing process. On occasion, such assessments cause reappraisal of the route that, if timely, can redirect the project to considerable advantage—to a superior variation within the same basic route or to a substantial change to a hybrid chemical scheme and, less frequently, to abandonment for another route.

> Preferably, the synthesis route is settled not late during this stage, but it is not all that rare, in the higher caliber process efforts, for that "better route" to come through and displace the prevailing route just in time to switch the scaled-up preparative work.

It is at this stage of merging chemistry and engineering efforts that the process development effort generally settles onto the right track and approaches critical mass. Process development organizations that lack the requisite engineering skills or that tap into relatively distant skills (say, from a technical resource in manufacturing) are at a marked disadvantage with respect to choosing the better process, since the said assessments are not done, are done less effectively, or are done without the criticality of mass that the occasion demands. The distant engineering skills are also far less persuasive when their assessment of the proposed synthesis is not favorable.

All seasoned practitioners of bulk drug process development know from at least one experience the very high price paid when the wrong process gets too far down the development cycle, and retreat is either unacceptable or very costly to the overall development timetable—thus the compelling need to make the fundamental choices of route, and of process approach within the route, with the full set of skills and address the key questions:

1. What will the commercial plant look like? What will its operation be like?
2. What are the probable capitals costs? How long will it take to be ready to start up?
3. What are the scale-up issues? Can they be addressed on time?
4. What is the environmental impact? Is there a good fit with the likely plant sites?

Once the bulk process team gets past this juncture with an action plan, the rest of the development stage is mostly a matter of good execution by all the disciplines involved. Although the analytical R&D function has not been mentioned up to now, its role is, of course, pervasive throughout—first in support of the early preparative work (a duty that remains with the function for the rest of the development cycle) and then in decisive and indispensable participation of the development activity at the bench and in the pilot plant.

Biosynthesis processes, which are based on fermentation processing in which the microorganism does the synthesis, face the same set of development issues but in a narrower field of options. Not only is the biosynthesis well defined and fixed by the microorganism, but alternate microorganisms with radically different pathways that could be more desirable are not that available. Chemical entities of natural origin are secondary metabolites of microorganisms or plant cells, and variations in the metabolic pathways that lead to a given secondary metabolite are relatively narrow compared with the many variations by which a compound can be made by chemical synthesis.

In this case, the development team (microbiology and biochemical engineering) aims at coaxing the organism or plant cell to be more effective. Strain mutation is a proven technique for improving the productivity of microbial biosynthesis and plant cell processes, although very few in industrial practice also seem amenable to increased productivity by manipulation of the cell lines and fermentation conditions. The microbiologist and the biochemical engineer are thus able to offer the potential for increased fermentation output by factors up to an order of magnitude or more—a potential not to be matched by increased yields from an organic synthesis. Indeed, some fermentation processes can go into manufacture at low titers with a high probability that increases will be obtained with continued development of the microbe or plant cell, as well as the fermentation conditions. Thus, variations on the biosynthesis—unlike variations on how to chemically synthesize a compound—are modest in range but not in significance to fermentation productivity (e.g., use of phenylacetic acid as a precursor in the fermentation of penicillin G) or other important aspect of the process (e.g., switching to a different *Taxus* plant from which a precursor to paclitaxel, comprising the taxane ring with all of the desired stereochemistry, could be extracted and chemically converted to paclitaxel at an advantage over the prior extraction of paclitaxel).

It is in the processing downstream of the fermentor that development possibilities become numerous, as a wide range of unit operations for concentration, purification, and isolation exist, just as wide as the processing options for recovering the desired compounds from streams (i.e., materials) issuing from chemical synthesis. This is discussed much further elsewhere in this chapter.

b. It is also in the *development* stage that the preparative work is scaled up in earnest with two purposes: (*i*) greater output of the bulk drug and (*ii*) the identification and resolution of the problems of scale attendant to the desired process. Although the latter goal requires that the desired route be at the scaled-up stage, considerable progress can be made if pieces of the desired route are scaled up before the total route is brought to the pilot plant.

c. It is also during the development scale that the definition and achievement of the desired physicochemical attributes of the bulk drug is pursued in earnest, hopefully after the dosage form development team has narrowed down the ranges for those properties after the major decision—which particular salt or the free base or the acid will be the bulk drug form of the biologically active structure. Such a decision may come late in the cycle, for oral drugs in particular, as the search for the desired bioavailability and stability may be arduous (14).

d. Finally, it is during the *development stage*, preferably early, that the bulk development team starts its work with the appropriate downstream organization in anticipation of successful drug development, registration, and market launch. This set of activities takes place in a rather distinct track from the R&D track, often placing inordinate demands on the bulk process team, as its obligations to the drug development effort remain unaltered by the onset of its obligations to eventual technology transfer.

> There is a great deal of risk when bulk process resources are badly caught in the vise of the demands from their drug development partners and the increasing demands of technology transfer. Staffing of the bulk process team—the engineers in particular—needs to recognize that successful drug development brings with it technology transfer. Unfortunately, R&D management and the peers in the drug development program are often insensitive or oblivious to the situation, and the cross-functional coordination team needs to be indoctrinated accordingly. It is very helpful to have the downstream functions related to manufacturing participate in the coordination team and thus ensure that those demands get known, if not fully appreciated.

In summary, Figure 11 depicts the *development stage* in the now familiar know-how versus applied effort plane. It is also timely to present the full spectrum of the bulk drug development disciplines and all the activities that they carry out, including those shared with others in the corporation or with outsources, as shown in Figure 12.

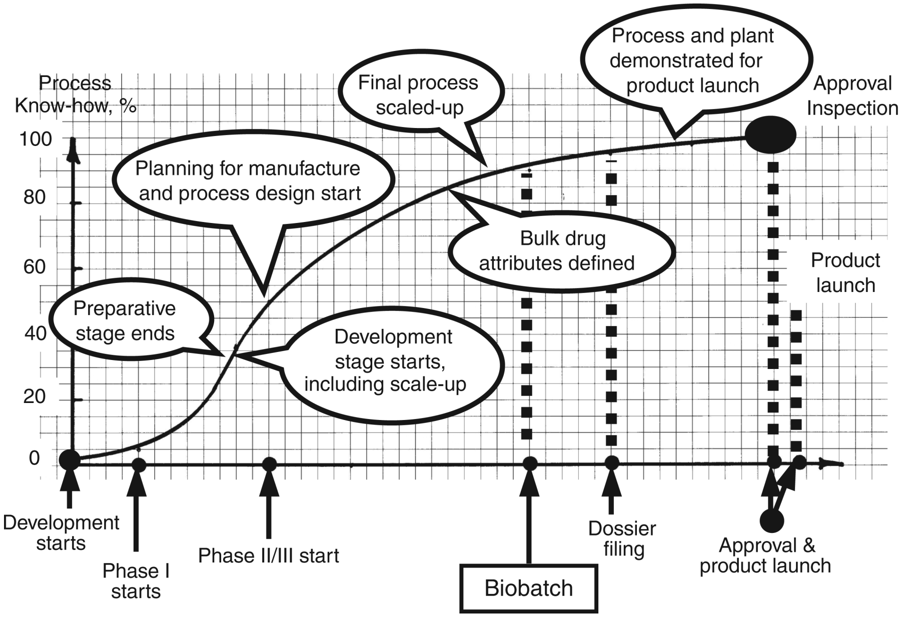


FIGURE 11 The development stage in the know-how versus applied effort plane. The principal process development milestones are shown.

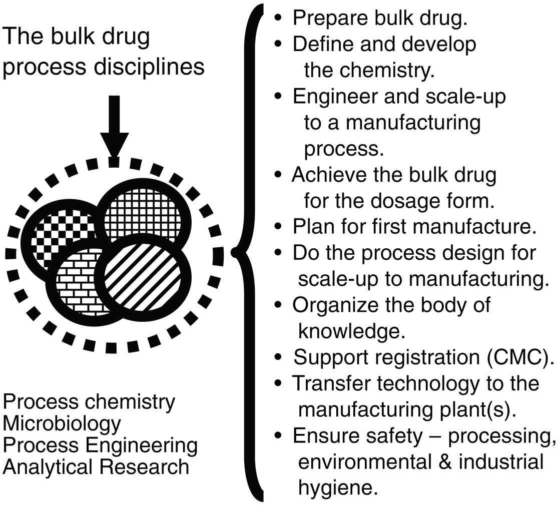

The bulk drug
process disciplines
Process chemistry
Microbiology
Process Engineering
Analytical Research
• Prepare bulk drug.
• Define and develop the chemistry.
• Engineer and scale-up to a manufacturing process.
• Achieve the bulk drug for the dosage form.
• Plan for first manufacture.
• Do the process design for scale-up to manufacturing.
• Organize the body of knowledge.
• Support registration (CMC).
• Transfer technology to the manufacturing plant(s).
• Ensure safety – processing, environmental & industrial hygiene.

FIGURE 12 Disciplines and activities in bulk drug process development. *Abbreviation*: CMC, chemistry, manufacturing, and control.

3. The Consolidation Stage

Although it is not infrequent for a significant bulk process "loose end" to remain tenaciously loose until late in the cycle, by and large the development cycle reaches a stage at which the more difficult development work has been done, to wit:

a. The chemical synthesis route is fully defined, albeit sources and specifications of starting materials may still be under negotiation or definition.
b. The actual process based on the synthesis route is sufficiently defined, and sound pilot plant operating procedures exist or are clearly in the offing.
c. Preparative support to the drug development program, although continuing and never leisurely, is no longer threatened by uncertainties about how to prepare the bulk drug.
d. Thermochemical safety data are firm, and only updating for process changes remains to be done. All issues are being dealt with adequately in the process design of the manufacturing plant.
e. The environmental impact of the process at the site of manufacture and at large is understood and acceptable, meeting company policy objectives. Obtaining all the requisite permits is likely.
f. IH issues specific to the process are understood and being addressed adequately in the process design of the manufacturing plant.
g. The process design, and possibly plant construction, is proceeding. Uncertainties seem within the grasp of the combined development/process design effort, and work can be focused accordingly.
h. Analytical methods for in-process and bulk drug control have been largely defined and remain to be confirmed and validated. Absolute purity, impurity profile, and crystal form are settled matters.
i. The scope and approaches to the dossier are largely in hand, if not in text.

There is, of course, no suggestion of the work being completed. Far from it, the *consolidation stage* is intense in a different way than the *development stage*. A

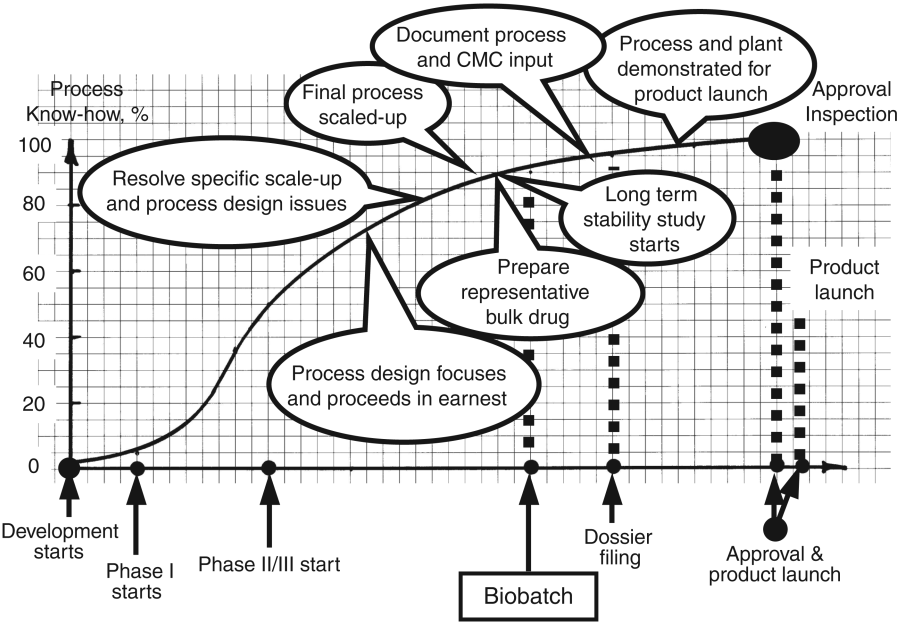


FIGURE 13 The consolidation stage in the know-how versus applied effort plane.

great deal of the work ahead is filling blanks (few if the prior work has been done well), refining pilot plant procedures, and catching up on the documentation that will support the dossier. Also, the final work on the definition and achievement of the bulk attributes needs to be done to support the final work on the dosage form side and the biobatch and stability studies that will follow.

There is also the largely increased workload in preparation for technology transfer, usually requiring frequent travel, a great deal of interaction, and the pursuit of much detail. Snags in process design and plant construction do come up, and environmental permits may require scrambling for some data.

However, the slope of the know-how curve is decreasing rapidly, as the bulk process is being implemented more than it is being developed, the loose ends notwithstanding. In summary, Figure 13 depicts the *consolidation phase* in the know-how versus applied effort plane.

4. The Technology Transfer Stage

Most of the discussion on the nature and scope of the technology transfer activity is presented in chapter 3. Nevertheless, the following seems pertinent at this point, as it relates to the technology transfer burden that the bulk process development team carries in addition to its duties on the drug development program.

a. A finite effort, even in the midst of a very difficult *development stage*, must be allocated to looking ahead to the specifics of manufacturing the bulk drug. This has been indicated in Figures 11 and 13.

b. The bulk process team needs to keep the rest of the R&D organization, its peers in the coordination team in particular, aware of this downstream task.
c. The technology transfer team needs to be well rounded—chemists or microbiologists, engineers, and analysts—and at the site of technology transfer. Staffing and briefs to do the job should be generous to decisively start up the process for product launch. No rescue missions allowed!
d. Successful technology transfer—from early planning for manufacture, process and plant design, process start-up preliminaries, and the actual demonstration that the process works in the commercial plant—rests squarely on the process body of knowledge being as complete as needed by the task and organized to effectively impart knowledge to the downstream organization.
e. Regardless of what organizational arrangement might exist, the bulk process development team needs to assume, hopefully in a collaborative understanding, a leadership role as the bringer of the know-how.
f. With the necessary adjustments, all of the preceding activities apply when transferring the process technology to contract manufacturers or licensees. More on this will be covered in section "Outsourcing in Bulk Drug Process Development."

III. FROM THE BENCH TO THE PILOT PLANT AND BEYOND

A. Process Conception and Bench-Scale Development

Except for fermentation or recovery from natural sources, all other chemical entities are obtained by chemical synthesis from organic chemicals and the process conception starts with that of the synthesis route—the scheme by which selected starting structures are converted to the target drug candidate. Factors considered by the synthetic chemistry team are as follows:

a. Starting materials that are available (or could be available) and promise an attractive route, and a wish list for such a route could be as follows:

    1. The route is direct, with few steps needed to reach the target compound.
    2. It is also convergent (two moieties can be assembled in parallel, then joined near or at the target compound), thus offering shorter synthesis cycles and higher yields.
    3. If chirality is sought, it appears attainable through enantioselective methods.
    4. Once obtained, chirality is preserved through the route.
    5. There is minimal need for blocking/deblocking.
    6. Highly hazardous materials, reactions, or intermediates are absent.
    7. An environmentally benevolent process is sought (i.e., *green chemistry*).
    8. Probable cost is appropriate to the product.
    9. The synthesis route fits nicely with existing plant running a related process.

The relative priorities of these factors vary widely, as they are seldom all present; neither are they fully independent from each other. For example, directness of synthesis may come at the price of a very expensive reactant or would require that a very hazardous intermediate be made and perhaps isolated. Or perhaps the greenest route seems least feasible. Additionally, the selection may be constrained by compelling demands of the drug development program: for example, the most attractive route would take longer to be ready for preparative work and development; it has to defer to the lesser route that can prepare the bulk drug now—not an uncommon juncture and decision, although it can be subsequently reversed.

Indeed, there is no established system to deliver the best or even a very good choice of synthesis route, and creativity and synthesis acumen still dominate, although obviously aided by the above and other simpler criteria, such as that of "atom economy" (how many atoms of the reactants end in the final compound?) (15). Occasionally, the choice is facilitated by a compelling case of an ideal starting material availability (e.g., a chiral intermediate that would bring all or a good deal of the target chirality with it), a selling approach that fine chemical producers exploit. Then at some point soon, the leading choice of route needs to be challenged by the various engineering assessments described in list "a" under section "The Development Stage."

Bench development of the route (or routes) of choice is pursued aggressively, ideally by both synthesis chemists and chemical engineers, with the former elucidating reaction pathways and by-products, seeking superior reaction conditions (solvents, catalysts, auxiliary chemicals, temperature, pressure, concentrations, reactant ratios, and approximate kinetics), as well as probing workup and isolation methods. The engineers work, in collaboration with the chemists, on aspects of the chemistry better suited to their skills (e.g., kinetics and thermochemistry, multiphasic reactions systems with mass transport effects that distort the chemistry, very fast reactions with selectivity issues that are sensitive to mixing, or reactions requiring concurrent separation or continuous reactors with tight control of residence time or extraordinary heat removal provisions).

Such bench development by both disciplines is what transforms a synthesis route into a process candidate for scale-up and eventual manufacture. If done concurrently—as it should be—it allows for the results to flow across the disciplinary boundary, shortening the path to a sound process derived from a sound choice of route.

b. Fermentation or natural product extraction processes, on the other hand, are not burdened by a broad range of route possibilities, as discussed in list "a" under section "The Development Stage." Bench development by microbiologists and engineers, however, is indeed rich with possibilities, to wit:

For microbial or plant cell fermentations

1. Elucidation of the pathway to the secondary metabolite
2. Nutrient, precursors, and optimization of fermentation cycle conditions (from the previous results)
3. Strain and cell line improvements with respect to productivity and robustness in fermentation
4. Data gathering to support scale-up to stirred tanks at all pilot plant scales
5. Definition of the downstream process candidate for recovery, concentration, purification, and isolation of the target product from the fermentation

For extraction of compounds from natural sources (plant or animal material)

1. Evaluation of differing sources of the compound bearing materials
2. Pretreatment conditions for successful extraction
3. Extraction or leaching conditions, solvent or extracting stream (i.e., material) selection, and separation of spent plant material
4. Definition of the process candidate for concentration, purification, and isolation
5. Data gathering to support scale-up

Most likely, both technologies eventually have to deal with relatively large volumes of cell mass or plant material waste, and bench work to address those issues is also needed.

B. Process Scale-Up

1. *What Is Scale-Up?*

At its simplest, scale-up is the set of processing issues that arise when the same operations take longer to execute in larger-scale equipment than at the bench scale. Although such issues do arise, they can be anticipated and in most cases avoided or largely mitigated through changes to the design and operation at the larger scale.

Much more often and less apparent, however, are the processing issues created by operating at a larger scale—*with greater dimensions and different geometries*—and thus affecting flow regimes, phase separation rates, interfacial surface areas, mass and heat transfer rates, flow patterns, heterogeneity in process streams (i.e., materials), and many other dimensionally sensitive variables and parameters. These effects are not related to a different time scale of processing events but arise instead from strictly physical effects that distort the process results from those at the small-scale baseline, including chemical outcomes. Relevant examples are as follows:

a. Reactants to a system of fast reactions cannot be mixed fast enough, and fractions of the reaction mass proceed for finite times at concentrations very different from the intended average concentration (some fractions are unduly rich in the reactant being added, while others are unduly low), resulting in a product distribution different from that predicted by the kinetics or obtained at the smaller scale.

b. Mixing in larger stirred tanks, if not adjusted properly, can result in significant differences in the composition of matter of multiphase process masses across the tank volume relative to the more uniform results in smaller tanks.

c. Rotating devices of larger diameter, such as agitators and pump impellers, as well as internal moving parts in a solids mill, will exhibit higher tip linear velocities and thus generate greater shear stresses in fluids or contribute greater energy to impacts relative to the analogous operation at the smaller scale.

d. Crystallization processes at a larger scale can suffer from unwanted nucleation as the result of heterogeneities in solvent phase composition during semibatch addition or in local temperatures upon cooling, as well as be more prone to crystal attrition and contact nucleation from the higher tip speed of the agitators and greater energy impacts among particles.

e. Transfer rates of sparingly soluble gases into liquids in stirred tanks generally suffer with increasing scale of the tank unless provisions are made to mitigate the differences, as the gas bubble size distribution (and with it the interfacial surface area) generated by the agitator impeller is different. Hydrogenation rates observed in laboratory pressure vessels, for example, most often do not scale up to pilot scale–stirred tanks because of the extraordinary gas absorption obtained in the liquid vortex at the lab scale; the larger pilot scale tank, being equipped with baffles, does not generate a vortex and that contribution to gas absorption is not present.
f. Large process vessels lose heat less rapidly than smaller vessels at the same internal and ambient conditions and, when deliberately cooled, will cool less effectively absent a mitigating cooling provision.
g. Larger flow contacting vessels for devices for gas-liquid, vapor-liquid, solid-liquid, and liquid-liquid systems will perform less well because of maldistribution, and bypassing of the phases worsens as the cross-sectional area of the contacting vessel increases. Such scale-up requires that provisions be made with internal parts to alleviate maldistribution.
h. Flow vessels will exhibit different flow patterns and residence time distributions than smaller vessels, which need to be taken into account so as to design the larger vessel accordingly.

Indeed, carrying out a processing operation at a sufficiently larger scale often shifts the rate controlling step of the process event *from one domain to another*. As an example, in reactions in gas/liquid systems, the small scale usually permits the reactant in the gas phase to be abundantly available to the liquid phase (the rate of chemical kinetics is observed, *as the gas/liquid mass transfer is not limiting*). Whereas upon scaling up, *the gas/liquid transfer may become limiting*, and the reaction, now starved for the reactant being supplied by the gas phase, does not follow its expected kinetics. The result of such shifts may go beyond the different rates of reaction, as selectivity (and relative rates of impurities formation) may change upon lack of a reactant. Generally, chemical reaction systems that have very fast rates or that take place in multiphase systems are sensitive to the operating scale due to the intrusion of mass transfer effects upon the performance of the chemical kinetics.

The above partial list provides frequent scale-up issues that arise in bulk drug processing with consequences of lower chemical yields or, worse yet, loss of control over the impurity profile, as well as slower processing, excessive damage to microbial cells and crystalline solids, undesirable particle size distributions, and any from a wide range of assorted shortfalls in process performance.

Understanding, *predicting*, and dealing with these issues require more than a modicum of chemical engineering skills, such as fluid mechanics, mass and heat transport, the use of dimensional analysis tools and mathematical methods for the simulation of events in a new context. Absent those skills, scaling up will result in surprises, cause much less effective troubleshooting, and engender an unwarranted fear of scaling up. Indeed, such apprehensions are now codified in arbitrary batch size ratios beyond which regulatory constraints to process change apply.

> Often enough scale-up is done much too tentatively, inserting intermediate scales that are not needed. Direct scale-up from the lab to the plant is quite feasible in a number of cases (e.g., fast liquid phase reactions with known kinetics and thermochemistry). All that is required is that the issues be understood and the proper parameters reproduced or improved at the large scale, using adjusted process conditions, as it is the set of the defining parameters what needs to be reproduced, not necessarily each process condition.
>
> Failure to understand scale-up issues equates a change in scale with a change in the process. While it is appropriate for a change in operating scale to come under the scrutiny of a well-managed change control system, there should be no assumption that it is "the process" that is being changed—a distinction that is not about semantics but about the approach to scale-up by the practitioner. This pertains in particular to operation of a pilot plant, in which scaling up and changing the process are a daily overlap that, if not practiced with a sufficient understanding of what is happening, will often befuddle the practitioner.

Yet, scale-up is inevitable, even in the relatively low-throughput environment of bulk drugs. Skillful use of the pilot plant environment, by which the preparative task and the process development scale-up coincide in time and place, is essential to a vigorous bulk development program lest the activity oscillate between the extremes of unskilled scale-up and feared scale-up. Indeed, lack of sufficient scale-up skills is a major disadvantage in bulk drug process development.

2. Tools for Scaling Up

In addition to the engineering skills and the access to the full range of supporting laboratory capabilities (bench development; in-process, analytical, and physical chemistry; microbiology), scaling up requires a variety of measurement apparatus (e.g., a compressibility cell to measure flows through beds of solids at different compression), as well as the frequent assembly of dedicated apparatus or pilot units (e.g., units to measure fouling rates of surfaces over short-term tests, small-scale centrifuges to more reliable measure centrifugation rates, leaf test units for vacuum filtration tests). It so happens that often enough some studies and measurements cannot be made in processing equipment nearly as well as they can be made in a smaller scale apparatus dedicated for the purpose at hand. The enterprising scale-up team will, in due course, assemble and accumulate such test apparatus as the needs arise.

In addition, some scale-up work needs apparatuses that are operated for preparative purposes as well, along the lines of the kilo lab, but in a flexible environment not focused exclusively on batch processing as the kilo lab is. Examples of such apparatus are fluid bed crystallizers, hydroclones for the evaluation of that method of solid/liquid separation, lyophilization cabinets with special vial sampling capabilities, and intermediate scale membrane processing assemblies. An area well suited for such testing purposes is not only highly desirable but often facilitates preparative work by processing methods not within the scope of the kilo lab. Such an area should be reasonably open for the manipulation of portable equipment, with ample walk-in hoods and tall

California racks, well distributed utilities, portable measurement panels for recorders, flowmeters, and the like.

C. The Pilot Plant and Its Objectives

The objectives of the pilot plant environment in bulk drug process development are simple:

1. Provide ready access to scaled-up processing for the bulk drug preparative effort.
2. Give the preparative effort a responsive environment to deal with the vicissitudes of the drug development programs being supported.
3. Permit the rapid and convenient evaluation of processes, methods, and equipment, as well as the mastery of their scale-up.
4. Obtain process data to support process design and the development of procedures for the eventual manufacture of the drug.
5. Demonstrate process performance at a scale that minimizes risk and the need to trigger scale-up constraints upon first manufacture.

Of these objectives, only the last seems to require elaboration at this point, as process design is amply discussed in chapter 3. Thus, given a sufficiently large scale of processing in the pilot environment where the development effort takes place, the transfer to manufacture will be far less likely to entail scale-up risk and, more importantly, far less likely to create a regulatory scale-up issue upon first manufacture. Bulk drug pilot plants of recent construction at R&D drug companies and at the major contract manufacturers provide batch processing vessels up to 10,000 L for chemical work and up to 20,000 L for fermentation work.

Table 3 outlines the equipment capabilities for a broadly capable bulk drug pilot plant, such as can be found in the major drug R&D companies, albeit not necessarily in the same location. Such plants have generally resulted by accretion and as needed to support vigorous drug development programs, say, no less than 30 compounds among preclinical and all phases of clinical work. Indeed, pilot plant capabilities of a similarly broad scope can also be found in the premier contract manufacturing companies, as they are active participants in the preparative work for the whole spectrum of drug R&D companies.

> Although in the 2000s the outsourcing field is populated with a great many small firms claiming to have cGMP pilot plant capabilities, Table 3 and the desired capabilities listed just below make it clear that the drug development business is one in which size does matter and matters greatly. Obviously, there is a sliding scale of capabilities versus scope of physical plant, and Table 3 describes its full range so as to decisively accomplish all of the previous aspects of pilot plant work for bulk drugs. Lesser options entail lesser preparative power, narrower range of scale-up and processing technologies, and processes tailored to fit existing capabilities. Alternatively, a combination of outsourcing and in-house resources can be used but most often with far less agility of preparation and development.
>
> Physical plant by accretion means that short of large lumps of capital investment, the processing capabilities will span designs and practices evolved over decades. However, issues of IH and regulatory expectations have gradually done away with open processing areas and rows of vessels in favor of processing modules in various degrees of segregation and connectivities. Figure 14 describes one such prototype of modular design for bulk drug chemical processing.

TABLE 3 Physical Plant of the Comprehensive Pilot Plant for Bulk Drug Processing

This table attempts to list most, if not all, of the equipment for a *comprehensive* bulk drug pilot plant. Accordingly, it is a wish list requiring a great deal of capital investment for fulfillment. Nevertheless, such pilot plant "complexes" do exist, arising mostly by accretion over decades, but also from projects of large scope used to augment and modernize earlier physical plant obtained by accretion. Pilot plant investment is generally viewed by R&D management as strategic, reflecting their long-term assessment of the vigor of the new drug pipeline, as well as their unwillingness to accept preparative bottlenecks. A proven overall physical environment is shown In Figure 14.

Some capabilities are needed very infrequently and are best secured through vendors, other companies, or universities that might possess them. For example, molecular distillation, high-vacuum fractionation, gas-solid elutriation at scale, fluidized bed crystallization, gas-solid catalytic reactors, vacuum belt filters, gas-solid ball mill reactors (a la Kolbe), very high pressure stirred autoclaves, and similar equipment. However, some projects reach the point at which the case for the in-house capability becomes compelling, particularly if the technology at hand seems attractive at large. Examples of such technologies are fluidized bed crystallization for the resolution of enantiomers, gas-solid catalytic reactors for selective oxidation or dehydrogenation of heterocycles, permeable wall tubular reactors, and membrane-aided liquid-liquid extraction.

Similarly, highly specialized capabilities and new technologies are best provided at an intermediate bench/pilot-scale for ready evaluation of whatever advantage might drive the larger-scale proposition. This is a large part of the rationale for the "bench/pilot" processing area, list 9: "Intermediate Bench/Pilot-Scale Lab for Engineering Studies."

For the smaller organizations, the appropriate pilot plant capability presents a formidable challenge. Preparative power and the ability to handle varied and often unpredictable processing tasks hinge on owning or having ready access to a sufficient breadth of processing equipment, preferably in a context amenable to experimentation at scale. Absent these capabilities, the processes so developed are, inevitably, highly constrained in their scope and technical ambition; compromises are inevitable, and timeliness and assurance of bulk drug preparation trump any other consideration. As to outsourcing as an adequate complement, its limitations are often severe, a principal topic discussed in the section "Processing Responsibility in Bulk Drug Process Development."

Infrastructure

Warehouse space—partitioned and protected to meet cGMP and safety requirements
Materials handling suitable to the scale and scope of the processing tasks
Utilities systems or suitable distribution from site systems
    Steam (up to 11 atmospheres)
    Cooling water (variable temperature depending on the source and season)
    Chilled water (down to 5°C)
    Refrigerated coolant (down to −25°C)
    Compressed air (up to 5 atm)
    Nitrogen (up to 2 atm)
    Portable hot fluid recirculating system (up to 250°C)
    Portable cryogenic recirculating system (down to −100°C)
    Electrical power (AC of normal voltage and of voltage required by industrial motors, e.g., 110–440 V in the United States)
Fire protection (no less than that required by the applicable codes)
HVAC (rather variable according to space being ventilated)
Tank farm (solvents, acids, bases)—all above ground, dikes as required

Pollution abatement systems (may vary widely in scope according to site circumstances)

Acid-base neutralization capabilities (at source)
Scrubbers (water and aqueous base) for the processing areas
Carbon adsorption systems for specific emission points
Trim condensers as required in processing vents
Thermal oxidizer and stack for process vent emissions
Tanks (segregated by waste category, dikes as required)
Ducting and fans for tie-ins to the various abatement systems
Hazardous waste storage and unloading to haulers

(*Continued*)

TABLE 3 Physical Plant of the Comprehensive Pilot Plant for Bulk Drug Processing (*Continued*)

Chemical processing areas

Nine distinct processing areas should be considered during the design or longer-term planning of a comprehensive pilot plant for bulk drugs:

1. *General chemical synthesis processing*. Processing duties that do not fall squarely into any of the following areas.
2. *Finishing area for bulk drugs (includes solids processing).* Light chemical processing, if at all. Key duties of this area are to crystallize the final compound as the bulk drug (with the desired chemical and physicochemical attributes). Includes filtration, drying, milling, classification, compacting, blending, and packaging. The environment is distinctly cleaner that most other areas.
3. *Aseptic finishing area for bulk drugs (includes solids processing)*. No chemical processing other than salt formation. Includes all of the above finishing area provisions, but largely in an aseptic processing environment for the preparation of sterile bulk drugs. Requires sterilization equipment, special ventilation systems, and much greater partitioning of the space.
4. *Hazardous processing for toxics, hydrogen, nitration, sulfonation, etc.* Segregated operating space with extraordinary fire, explosion venting, and ventilation provisions. Contains the key equipment for reaction and limited workup.
5. *Highly potent compounds processing.* General processing equipment in a segregated area and equipped for a high degree of containment of materials being handled, due to industrial hygiene and environmental safety reasons.
6. *Housekeeping (neutralization and other disposal activities with waste streams)*. Complements the above areas, sometimes being within or adjacent (e.g., Fig. 14).
7. *Fermentation processing.* Very distinct in space, equipment, and auxiliary facilities (16). Microbiology lab, seed development lab, and fermentor train. Air compression, air and liquids sterilization, tank and piping sterilization. Stirred tank fermentors, feed tanks, and harvest tanks.
8. *Downstream processing of fermentation streams.* Also a very distinct processing area: little chemistry but a great deal of workup, purification, and isolation with a different mix of unit operations (17).
9. *Intermediate bench/pilot-scale lab for engineering studies* (not the kilo lab, although it can be readily pressed into preparative duty as appropriate). Multilevel open bay space, walk-in hoods, tall racks, utilities stations for rented portable equipment, and very little fixed equipment.

Clearly, each of these areas has different requirements, but it is not in the scope of this chapter to attempt a discussion beyond the above outlines (18).

Processing equipment

General purpose stirred vessels in the 100–5000 L range: glass-lined/316L stainless steel/specialty alloy in an approximate ratio of 1/0.4/0.1 in frequency. Vessels above 100 L should have split jackets. All vessels intended for a processing function (as opposed to waste neutralization, solution makeups, etc.) should have variable speed drives for their centerline agitators and be baffled accordingly. Vessel layout and connectivity can vary widely, but organization into multipurpose once-through gravity modules seems to be the most useful for piloting purposes (i.e., from top to bottom levels: setup, reaction, workup, crystallization and solid-liquid processing, and housekeeping) (Fig. 14).

Within the category of general purpose vessels, a variety exists that the design can put to good use. For example, vessels intended for crystallization will often have agitator impellers better suited for that purpose, or vessels intended for workup of reaction outputs will often be fitted with auxiliary devices for liquid-liquid extraction or for evaporative concentration.

Fixed auxiliary equipment for general purpose stirred vessels (sized accordingly): condensers, decanters, receivers, weighing tanks, solids charging devices, sampling devices, pumps and piping, connectivity to the tank farm and to pollution abatement equipment, connectivity among each other, vacuum sources, vent trim condensers, overhead catch tanks, in-line filters, flow splitters, etc.

Portable auxiliary equipment for general purpose processing: pumps of various kinds (centrifugal, positive displacement, vacuum), drum handling devices with pumping provisions for charging to vessels, scales of various ranges, stirred tanks (slant agitator) in the 100–1000 L range, recirculating sampling or sensor loops, small filter press or pressure plate filters, blow charge tanks, line mixers, etc.

Specific processing equipment and their auxiliary equipment (as above):

a. *High-pressure reaction stirred vessels* (glass lined up to 5 atm, 316L stainless or specialty alloy to 15 atm).
b. *Liquid-liquid extraction and phase separation devices*: centrifugally aided, including those capable to deal with suspended solids (i.e., for fermentation broths processing); mixer settlers, membrane coalescing filters, extraction columns, etc.

TABLE 3 (*Continued*)

c. *Gas-liquid contacting devices* (other than pollution abatement devices): overhead venturi contactors, high-turbulence contactors, packed or tray columns, wetted wall columns, etc.

d. *Evaporation and distillation equipment*: falling film, long-tube and wiped-film evaporators with their condensing, receiving, and vacuum sources; fractional distillation columns with their accessories, vapor-liquid disengagement inserts in selected vessels, etc.

e. *Adsorptive processing equipment*: columns and accessories for ion exchange, chromatography, and other solid-liquid adsorption, high-performance liquid chromatography systems (columns, tankage, influent delivery devices, sensors, and controls), molecular sieve solvent dryers, etc.

f. *Solid-liquid separation devices*: centrifuges [center-slung dig-out (up to 24 in.) or bottom drop (up to 48 in.), horizontal axis, and side discharge], pressure and vacuum filters (stacked disk, plate and frame, agitated filter dryers), cross-flow filtration, polishing filters, etc.

g. *Solids drying equipment*: Tray dryers (vacuum and air), fluid bed dryers, vacuum tumble dryers (with assorted internals), stirred filter/dryers, countercurrent solids-gas dryers, spray dryers, lyophilization systems, etc.

h. *Solids processing equipment*: Fluid bed and rotating shell processors, assorted grinders and mills, compactors and extruders, classifiers and blenders, etc.

i. *Solids-liquid processing equipment*: homogenizers, colloid and ball mills, fluid bed and rotating shell processors, etc.

j. *Membrane processing systems*: cross-flow filters, ultrafiltration, nanofiltration, reverse osmosis, and pervaporation.

k. *Fermentors and auxiliary equipment*: stirred tanks with special cooling and steam sterilization provisions, designed for ease of sterilization and maintenance of sterility; gas sparging, higher than usual power inputs through agitation; air sterilizers; feed tanks of various sizes; liquid sterilizers (16).

l. *Portable equipment cleaning modules, clean-in-place provisions in many vessels, fixed cleaning stations.*

Process control capabilities

The bulk drug pilot plant must execute unusually varied processing with the requisite degree of control over the process variables, as well as have extraordinary means for data capture online (directly from sensors or analyzers in the equipment) and off-line (from samples tested in the laboratory and by derivation from raw data, e.g., the supersaturation profile of a batch crystallization, the performance of a fermentation cell mass from off-gas data analysis, the changes in the agitation requirements through the course of a reaction or fermentation, and the heat balance across a condenser). Indeed, pilot plant work provides the opportunity to gather engineering data on scaled-up process performance during development, thus facilitating the better process design decisions. Often enough, the scale-up data drive the development of the process in a different direction as well.

Accordingly, most vessels and other equipment are provided with the appropriate sensors (temperature, pressure, level, pH, rotational speed, flow rate, weight, conductivity, etc.) and on-line analyzers as required. Some of the sensors may be used for local read-out (the value of the process variable may be read at the location of the equipment) *and* as inputs to a process control system elsewhere (a control room where, among other things, the inputs are converted by the controllers to outputs to valves, switches and actuators in the field). The rest of the sensors may be used for local read-out and control (the control device is also at the location of the equipment), but may also share the read-out with the control room. The option of operating through local control exclusively, while still available in principle, is rather unlikely to be found, as even operating environments of modest scope have mostly strived for some degree of remote control.

A process control loop consists of these principal components:

A sensor for the process variable at the appropriate point in the process stream and equipment, for example, a thermocouple that generates a voltage as a function of temperature. The voltage is received by a transmitter (usually located at the equipment) that converts the voltage to a signal recognizable by the next device, for example, a current in the 4–20 mA range according to a preset calibration of temperature to voltage to current.

A controller (or control device) that receives the input signal from the sensor and transmitter, compares the value of the process variable with a target value (the set point), and sends out an output signal to adjust the variable as needed.

An actuator (a valve, a rotational speed drive, etc.) that, in response to the output signal from the controller, seeks to adjust the process variable. For example, the actuator may be a control valve that allows more steam to pass through and thus increase the temperature of the process materials in the equipment.

(*Continued*)

TABLE 3 Physical Plant of the Comprehensive Pilot Plant for Bulk Drug Processing (*Continued*)

This said, remote process control can be variously implemented, taking advantage of the many scopes of control systems that are available. Ambitiously, a pilot plant processing area will have most of its process and infrastructure variables controlled remotely from a central location, using digital control devices connected to, with many governed by, a substantial computer system. The computer system monitors selected process variables and controls many of those, relying on schemes that range from individual loops, for which the set point is entered at will to complete schemes (and their algorithms) that sequence and control the processing events from a master set of instructions (often referred by the unfortunate term "recipes") or maintain the readiness of the infrastructure (HVAC and utilities). Most ambitiously, as well as unwisely, the designers of the control system may reach out and link the system that controls the processing events with extraneous systems, such as those that manage in-process and QC data or those that manage materials inventories and procurement. Such excessive connectivity is not needed for process control or process data gathering but greatly increases the burden of the inevitable validation task. While perhaps of value in a large manufacturing environments, such linkages and data sharing marginally aid the pilot plant task at the cost of greater validation and system maintenance efforts.

Provisions for ascertaining the identity, lot number, and release status of materials, such as bar coding and the like, should not be viewed as excessive but should be well isolated from the direction and execution of process tasks. Indeed, the objective of the minimalist approach is to reduce to the minimum those connectivities that are superfluous to the basic task of *a pilot plant: simultaneously prepare material and develop the chemical process*.

Indeed, a very adequate and prudent approach is to delegate to local microprocessors (or programmable logic controllers) the lesser control tasks, for which modern equipment comes with fully developed and validated process control packages, for example, automatic centrifuges for filtration, manipulation of heating and cooling fluids in vessel jacket services, and HVAC management systems. In this lean approach, and *to the extent possible*, the supervisory process control system (at the top of the hierarchy) simply triggers the actions of subordinate systems, and during the period of action by the latter, it may monitor the appropriate process variables but does not control them. At the processing level, the subordinate systems do all the manipulations under the benevolent gaze of the top system and fade out of the scheme once the task is done; they do not link with the supervisory system except to acknowledge the instruction to start or indicate its completion. Also in this approach, the supervisory system operates at arm's length with any extraneous systems involved with materials or laboratory data management. The objective, of course, is to severely limit the range of unintended consequences associated with large sets of computer code controlling multiple tasks and manipulating large amounts of data. As the regulatory expectations on the integrity of control and other software-based systems approach the fastidious, simplicity in the design of schemes for process control and data management becomes compelling, and hopefully, there will be a persuasive minimalist among those making such design choices.

The qualifier "to the extent possible" recognizes the fact that certain tasks are beyond the ability of the individual equipment control package, as well as the desirability of setting up *at will* specific control loops and their set points, the sequence of events, alarms, etc.

Striving for such simplicity is not to be confused with the now-ascendant method of processing based on standard operating procedures (SOPs). In the latter, the execution of the processing can approach a veritable daisy chain of SOPs that minutely dice the overall task. In the extreme, the so-called manufacturing document (or whatever term might be used) becomes little more than a log, offering no perspective on the processing. Worst of all, operating personnel understand dimly at best what they are doing, and mining the document for troubleshooting or assessment information is tedious and often unproductive.

Portable control modules may also be used; these consist of recorders and controllers to create local loops with the appropriate sensors and valves or actuators. Specialized analyzers can be used on ad hoc or permanent basis for online analysis of specific process variables, often through a sampling loop.

A laboratory for in-process control testing must be equipped and staffed well, and managed to be responsive and convenient to the pilot plant processing areas. In the pilot plant environment, there is a large data-gathering component that often results in large loads of in-process testing relative to manufacturing operations.

TABLE 3 (*Continued*)

Finally, and still in the process control subject, it is important to provide the technical and supervisory staff with suitable and convenient office space and related work areas. In all chemical processing, regardless of the control scheme being used, the *eyeball contact* with the process operations is important. This is the case, most of all, for the bulk drug pilot plant, as a great fraction of the activities are being done for the first time and repetitive processing is so infrequent.

Training

Training facilities and unrelenting training are an indispensable part of a bulk drug pilot plant operation, aimed at safe processing, reliable preparation of bulk drug, and effective use of the opportunity to scale up the process and gather the desired know-how. Given the experimental nature of the pilot environment, those that run it need to be extraordinarily sensitive to the process to be run. In that respect, SOPs have a rather limited value, as only the most elemental actions are repetitive; today's batch incorporates significant differences from yesterday's and will be different from tomorrow's, even if performing the same basic process. Thus, training must be *based* on the fundamentals that can be effectively presented to all involved.

The increased use of SOPs, driven by a regulatory preference and the seemingly paramount objective of consistency, can, in the extreme, dice the operating instructions so minutely (approaching a daisy chain of SOPs) so as to make it very difficult for the operating personnel *at various levels* to fully appreciate the scope of the overall task and the linkages between its different parts. This, coupled with the prevalent use of great detail in the operating instructions, has led to documents that are unwieldy, replete with discontinuities, and very hard to use as training tools or for troubleshooting or retrospective data mining.

While undoing this state of affairs may, alas, not be possible, it is indeed possible and most advisable to preface the formal operating instructions document with a brief outline of the process and its procedure, written in clear prose (not instructions in the imperative mood) and accompanied by a flow diagram of the procedure in the context of the designated equipment, as well as including some brief discussion of the objectives of the work to follow. For example, a statement such as "Set up RE-302 for distillation under total reflux prior to the application of steam its jacket," an instruction that in today's documents may take a number of sub-instructions and no less than a page, conveys quite clearly the operational intent and was, at one time, quite sufficient for a skilled chemical operator. A preview of such preface by all levels of operating personnel has multiple advantages, including alleviating the insidious effect of the disrespect for the operating people implicit in the prevailing mode of operating instructions.

Abbreviaton: HVAC, heating, ventilation and air conditioning.

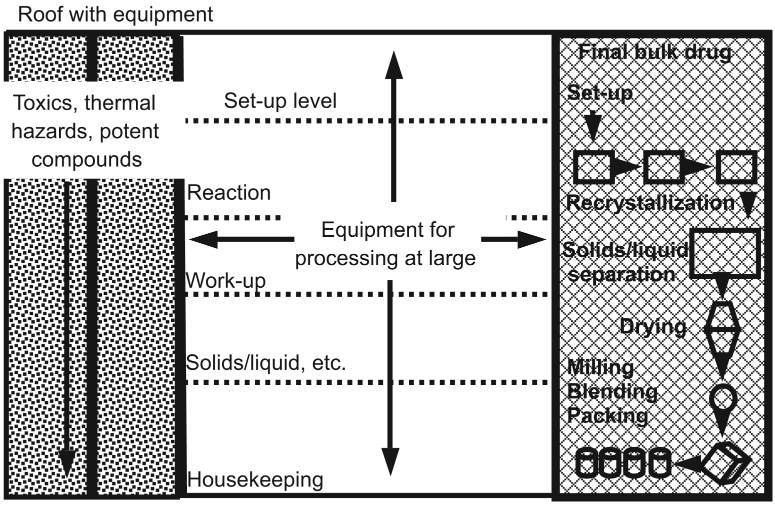


FIGURE 14 The multipurpose, once-through gravity plant for bulk drug processing.

Besides the physical plant there are, of course, other capabilities and attributes for a successful bulk drug pilot plant environment, to wit:

1. A skilled team of chemical engineers and chemists to operate the facility, with the depth to operate as a process development cadre, capable of addressing the full range of technical needs of scale-up and process design work as well as day-to-day operations.
2. Close collaboration and ready access to bench development chemists, microbiologists, and engineers who have project (drug candidate) responsibilities in the pilot plant as well. Whether by ready accessible or by being integral part of the pilot plant, an engaged and capable analytical laboratory is indispensable for full support.
3. A skilled team of chemical operators who are trained unceasingly in the fundamentals as well as in all that is new by way of equipment, procedures, polices, and applicable regulations.
4. A support laboratory for close and responsive in-process, troubleshooting, and quality assurance/quality control (QA/QC) support to the pilot plant operation.
5. Ready access to the analytical R&D function of the bulk process development area.
6. The appropriate lab capabilities as per 4 and 5 for fermentation processes. These differ markedly from those of chemical synthesis (16).
7. A skilled materials management function with the appropriate tools for materials tracking, documentation, and security.
8. A dedicated maintenance and minor installation team with adequate workshop and stores.
9. A skilled clerical support function, well trained on the regulatory obligations of the pilot plant operation and the requisite tools.
10. Internal skills in the environmental engineering field and the applicable regulatory milieu for the pilot plant facility, as well as ready access to the appropriate site or corporate functions.
11. Internal skills in the operational safety and IH fields, as well as ready access to the appropriate site or corporate functions.
12. Management systems and a managerial tone that foster and insist in safe and responsible operation, strict maintenance of the physical plant, continuous training, and strict regulatory compliance as called for by the developmental activity.
13. A management that fosters and maintains a pilot plant organization as a vibrant, engaged, and highly skilled component of a broadly based process development function in the bulk drug business. An indispensable obligation of pilot plant management is to ensure that no one forgets, under the pressure of serious operational and regulatory demands, that the pilot plant is an experimental environment with a major responsibility in the creation of the process body of knowledge.

Finally, and as indicated in Table 3, the pilot plant processing equipment needs to be set up and tailored to facile data gathering, well beyond the usual process variables measurements—extraordinary sampling ports and devices, nozzles, and flow loops set aside for the insertion of infrequently used sensors, recirculating sample loop modules, flow loops, etc. Modern pilot plants are usually well provided with process control systems that monitor, control, and have responsive sequencing capabilities. Such systems are very advantageous in what is, after all, an experimental environment. One needs to be alert, however, to the possibility of making the process control system too rigid in its operating procedures and thus discourage the enterprising experimentalist or data gatherer. Finally, the operating style of such a modern facility should still encourage old-fashioned eyeball contact with the process on the plant floor.

In summary, the bulk drug pilot plant is a critical mass of skills and capabilities within the larger critical mass of the bulk process development function. Obviously the size and scope of the organization matters a great deal—bulk drug pilot plants with capital replacement values of over a billion dollars and operating budgets well over $100 million per year exist. Nevertheless, and although difficult, pilot plants of lesser scope and ambition can be created *provided* the requisite skills and management systems are assembled cohesively and maintained well.

D. New Processing Technologies

The process development environment is optimal for the evaluation of new technologies and methods for bulk drug processing, as all the necessary elements exist and are well poised for the acquisition of new experience:

a. The aggregate of discipline skills
b. The interdisciplinary critical mass
c. The experimental capabilities at bench, kilo lab, and pilot plant scales
d. The working interfaces with process design and manufacturing

Yet, there is an element of risk that, albeit of a different character, may be seen as comparable to that encountered when evaluating new technologies in manufacturing. Whereas the latter is burdened with rigid regulatory constraints that may ultimately quarantine or preclude the sale of product made under test conditions, the pilot plant is comparably constrained, not so much because of regulations, but because of the risk to the supply of material to the drug development programs. This risk is, for all practical purposes, regarded just as large as, or larger than, lost manufacturing output, as there is a potential impact on the drug development timeline.

Alas, the seemingly obvious solution of evaluating new technologies on a parallel track does not work well enough. At some point the new technology or method needs to be reduced to practice at scale and the perceived risk arises—compromising the yield or quality of material made under the test conditions or usurping preparative capacity for nonpreparative purposes. In a vigorous drug development program, that capacity (technical personnel as well as equipment) is usually fully allocated. Furthermore, R&D management at large has no sympathy for such distractions—a utilitarian outlook that could be well justified.

The less obvious solution, however, is to evaluate the new technology in stages, not unlike a new process variation arising from the development work, such as a different starting material, solvent or catalyst, improved purification, or a faster and more reliable drying procedure for the bulk drug. These latter changes are routinely introduced to the preparative work in a deliberate manner but with the relative procedural ease that characterizes the pilot plant environment. R&D management knows, perhaps deep in its subconscious, that the bulk process development function merges the preparative work with constant scaling up of new methods and that a very large fraction of preparative work is also experimental. With discretion and with an extra measure of deliberation, new technologies can be similarly evaluated at no greater risk.

In that regard, the more experimental aspects of the pilot plant that have been described in section "Process Scale-Up" are very well suited. In addition, getting moral, as well as other, support from the manufacturing organization adds to the impetus and justification of the apparent distraction of bulk development resources. This is even more important to the technology stance of bulk drug manufacturing under the current and foreseeable regulatory environment that unwittingly discourages innovation into pharmaceutical manufacturing.

E. Beyond the Pilot Plant

As the *consolidation stage* comes to a close—slower pace of preparative work and having provided the body of knowledge contribution to the assembly of the dossier—the bulk development team shifts its focus to the technology transfer to manufacturing. Although its participation in the preliminaries started, or should have started, at the early *development stage* and continued, increasingly, through the *consolidation stage*, now that time has come to demonstrate the bulk drug process performance in the first manufacturing plant or plants, the latter in the event of multiple sites of first manufacture. In such cases, the bulk process is generally operated in one plant through the bulk drug, but a slip stream of penultimate compound (the final intermediate) or the final compound in unfinished form is shipped to another site for final processing to the bulk drug.

There is considerable material to cover on what happens beyond the pilot plant, and such is the subject of chapter 3.

IV. THE PHYSICOCHEMICAL ATTRIBUTES OF THE BULK DRUG

As one of the three basic tasks of bulk drug process development, defining and achieving the physicochemical attributes of the bulk drug is pursued throughout the development cycle. Unavoidably, this effort trails that of the chemical or fermentation process, since its target comes from the dosage form development effort.

The difficulty of the dosage form task cannot be underestimated. Its need for making judgments with partial data actually exceeds that of the bulk development task, as the crucial feedback on the bioavailability and stability of its developmental materials cannot be obtained rapidly, not unlike the feedback that the bulk development team needs as to the suitability of the bulk drug for dosage form purposes. Figure 15 is an attempt to depict the scope of dosage form development.

> Not to be neglected is the packaging development placed directly downstream from dosage form development. Sometimes complicated by the fact that the primary package (that in direct contact with the drug product) may also serve as a drug delivery device (e.g., syringes, eye drop dispensers, intravenous bags) as well as by the issues of interaction between the dosage form and the package's material or the long-term stability of the drug product within the particular package chosen, the dosage form development function is additionally buffeted by marketing issues that range from the serious (acceptability by the patient, for example) to the seemingly frivolous (e.g., the marketer's insistence on a distinct tablet shape that, although harder to manufacture, lacks an apparent redeeming value).

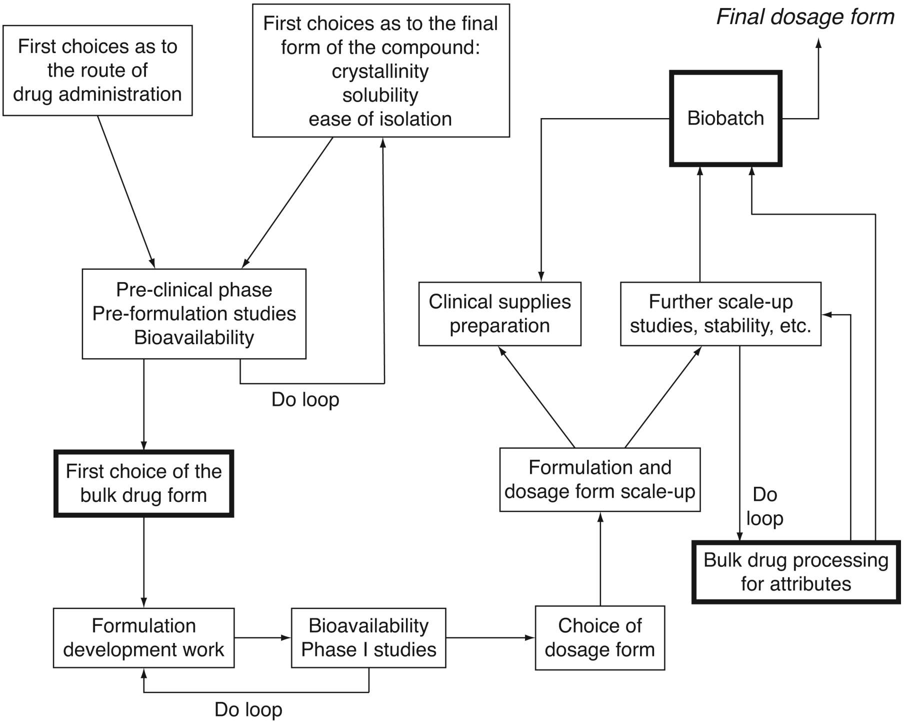

First choices as to the route of drug administration
First choices as to the final form of the compound: crystallinity solubility ease of isolation
Final dosage form
Biobatch
Pre-clinical phase Pre-formulation studies Bioavailability
Do loop
Clinical supplies preparation
Further scale-up studies, stability, etc.
First choice of the bulk drug form
Formulation and dosage form scale-up
Do loop
Bulk drug processing for attributes
Formulation development work
Bioavailability Phase I studies
Choice of dosage form
Do loop

FIGURE 15 The scope of the dosage form development task. The notation “Do loop” refers to the iterative process by analogy to the Fortran language shorthand.

Crystallinity is the key physicochemical attribute of a bulk drug, as it provides:

the optimal chemical stability in the large majority of the cases;
the best framework for purification after chemical synthesis;
the best opportunity to establish reproducible important physical attributes that

determine the consistency of manufacture, *bioavailability* and shelf life for the bulk drug and for most dosage forms:

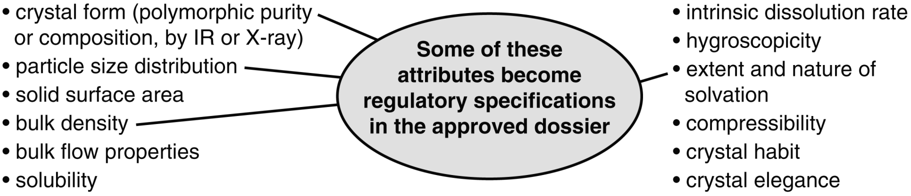

• crystal form (polymorphic purity or composition, by IR or X-ray)
• particle size distribution
• solid surface area
• bulk density
• bulk flow properties
• solubility
Some of these attributes become regulatory specifications in the approved dossier
• intrinsic dissolution rate
• hygroscopicity
• extent and nature of solvation
• compressibility
• crystal habit
• crystal elegance

FIGURE 16 The physicochemical attributes of a bulk drug.

Albeit hampered by a traditional disciplinary divide between pharmacy and the disciplines of bulk process development, the bulk/dosage development interaction needs to start early and intensely. Not only is the task difficult for the reasons just stated, but there is considerable scope to getting to a firm definition of what is needed. Figure 16 lists the physicochemical attributes of bulk drugs that must be controlled in the bulk drug process, either directly, such as particle size, or indirectly, such as solid surface area or hygroscopicity.

Those attributes are, of course, set by the very last processing steps of the bulk drugs:

a. The last synthesis step (or the last purification step if a fermentation/extraction process)
b. The subsequent isolation (usually by crystallization), filtration, and drying
c. The final solids finishing (size reduction, classification, blending, and packaging)

Due to the significance of the physicochemical attributes of the bulk drug to its bulk and dosage form stabilities, as well as to the dosage form performance (mostly bioavailability), it has become increasingly frequent to add *re*crystallization after the isolation of the final chemical compound and thus generate the *bulk drug*. Although such additional processing is expensive (its yield loss is incurred with the costliest compound), there are significant advantages to consider:

a. The final compound isolation is relieved from the dual burden of simultaneously achieving all the chemical purity attributes *and* all the physicochemical attributes.
b. The discontinuity makes the final bulk drug less subject to upstream variations from the more complex synthesis/purification/isolation step.
c. The final recrystallization can provide an additional degree of purification that may be reserved as insurance or be part of achieving the final purity.
d. The final recrystallization can be developed with a sharp focus on *consistent* attributes such as polymorphic content, crystal habit, particle size distribution, surface area, and bulk density. These attributes also define hygroscopicity and are important factors on bulk and dosage form stability.
e. Regulators are very fond of such recrystallization (for the preceding reasons), which can be used to more persuasively present upstream process changes for approval.

The addition of such final recrystallization is depicted in Figure 17. Given the fact that practically all bulk drugs are crystalline for reasons of processing soundness, purity, stability, and consistent physicochemical attributes, obtaining registration of a bulk drug in any other physical state usually requires a compelling reason.

> As practitioners discover (or should soon discover), crystallization skills are paramount among the skills set of the bulk process development (and manufacturing) function. Such skills should be nurtured, perhaps even lavished, as well as complemented with a comparable physical chemistry capability in the analytical R&D function.
>
> This seems a good point at which to define the analytical R&D function as far more than the guardian of quality during the preparative work or the highly skilled developer of assay and related methods or the arbiter of regulatory issues within the bulk process development. For successful bulk drug process development, the analytical R&D function must be an integral part of the *process team*: elucidation, troubleshooting, contributor to the solution of process problems, and intimate partner throughout. Any lesser involvement in the process task or lesser aggregate of skills is a strategic disadvantage in drug development.

Finally, the bulk process and dosage form functions need to collaborate earnestly at the earliest and, if needed, be brought together under irresistible

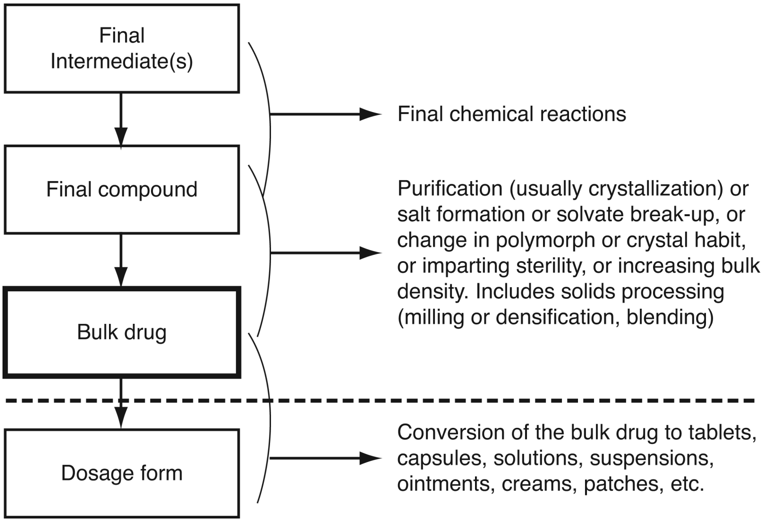

Final Intermediate(s)
Final compound
Bulk drug
Dosage form
Final chemical reactions
Purification (usually crystallization) or salt formation or solvate break-up, or change in polymorph or crystal habit, or imparting sterility, or increasing bulk density. Includes solids processing (milling or densification, blending)
Conversion of the bulk drug to tablets, capsules, solutions, suspensions, ointments, creams, patches, etc.

FIGURE 17 The final stages of bulk drug processing. A final crystallization is often inserted largely, if not strictly, for greater control over the physicochemical attributes of the bulk drug.

force to overcome the traditional disciplinary gap. Indeed, the crucial decision on which bulk drug form is to go forward (the sodium salt? The maleate? The dihydrate?) is best made when the bulk process team participates and is able to contribute its resourcefulness lest the dosage form team abandons the better bulk drug form because it did not know that its difficult attributes could be managed or fully overcome upstream. It is there that those attributes are set through the actual process in the final reaction step and in the finishing steps that follow to afford the final bulk drug.

V. THE PROCESS BODY OF KNOWLEDGE

In developing the process for a bulk drug, the need to gather and properly organize a process body of knowledge is compelling:

1. The dossier requires that the process foundation—chemistry, engineering, scale-up, bulk drug chemical and physicochemical attributes, environmental impact, process controls, preparative and developmental history, and bulk/dosage issues—be readily available and well organized for the assembly of the various individual submissions. Increasingly, these submissions need to provide a level of *bulk drug process validation*, namely, a persuasive case that, on the basis of the actual performance during the preparative and developmental effort, the process is capable of disciplined manufacture and thus results in bulk drug output that is consistently safe and efficacious.

   Additionally, the dossier should have the documentary basis for being able to include in the submissions a similarly persuasive case that the proposed manufacturing plans are generally sound—to wit, that the intended manufacturing milieu will do justice to the process needs as identified during its development. Such bridge *documentation*, while not relieving the technology transfer team from the burdens of whatever inspection the manufacturing plant may face, greatly facilitates the task of preparing for such inspection and for dealing with it if it occurs. Just as importantly, the said *bridge documentation* also provides the regulatory reviewer with sufficient background to answer a number of probable questions and thus avoid their being asked during the review cycle.

It is rather easy for practitioners, when faced with the previous tasks, to get thoroughly lost in the detailed "how-to" without fully grasping the scope and objectives of the dossier on the process, which have been defined earlier. As the literature on "how-to" grows and seminars, workshops, and guidance documents proliferate, the practitioner should first seek a clear understanding of what it is that the submission review and the plant inspection *basically* seek to accomplish. The preceding paragraphs are an attempt to clearly define just that, and additional background material, still at the usefully general level, is suggested (19,20).

2. The technology transfer to manufacturing demands that the process be well documented. Most important, and as a coalescence of the process know-how, a *comprehensive process document*, written for the specific purpose of imparting knowledge, is a requisite for the following tasks:

    a. Process design
    b. Project engineering design and construction
    c. Procurement of materials
    d. Preparation of start-up plans and operating procedures
    e. Transfer of the in-process and QC analytical methods
    f. Assessment of the process safety issues in the specific context of the plant: operational safety, IH, and thermochemical and environmental safety
    g. Assembly (and timely approval) of environmental and other regulatory permits
    h. Definition of the process start-up targets of yield, capacity, waste loads, etc.
    i. Dealing with other assorted matters, such as those arising from the plant's insurance.

    It is, of course, unacceptable to bind together all manner of development reports and send them over with a cover memorandum (part of what is aptly known as "over the fence" technology transfer). Attachments are very important, but a well-edited document that is rich in content and aimed at guiding the downstream practitioners is the indispensable first vehicle for the transfer of the know-how. Not even the most thorough collaboration between development and manufacturing can completely remedy the lack of the comprehensive process document intended for imparting knowledge.

There is no attempt here to gloss over the extraordinary effort and discipline required to turn out such documentation on a timely basis. The *consolidation stage* is intense, the gentle slope of the know-how curve notwithstanding. Yet, the quality of the technology transfer—on both the short and the long term—is very much enhanced if such a document is available soon enough.

Conversely, and as indicated in Figures 11 and 13, the joint effort with the operating organization (planning and process design) unavoidably overlaps the actual development of the process, sometimes to a great extent. For example, if an early decision is made to build a new plant or substantially alter an existing plant, the downstream work cannot await a sufficient definition of the process and information needs to flow as the process is developed. This is a very demanding task for all involved that benefits from considerable practice, significant skills of process design on both sides, and a spirit of collaboration, preferably steeped in previous joint successes. Unlike other chemical processing activities, new bulk drugs are exceedingly driven by the "time to market" imperative, and organizations that can significantly overlap process development with manufacturing readiness work have a strategic advantage. However, having such skills and practices does not relieve the development team from the duty of comprehensively documenting the process at the earliest reasonable time.

3. After successful technology transfer, which must, of course, be well documented also, the original process body of knowledge serves as the foundation for management of the change control system, for training of new manufacturing personnel, and as the basis for sound process improvement work. Indeed, significant second-generation processes are most often based on approaches suggested and partially elaborated during the original development.
4. Although the interaction with suppliers and contract manufacturers will be discussed more amply in section "Processing Responsibility in Bulk Drug Process Development," it is often that process information needs to be transmitted to outsiders, including prospective licensees of the drug candidate. Indeed, this happens most likely during the developmental phase as help is sought in the preparation of intermediates or the bulk drug itself or in further development of the process or an alternative route for which the outside collaborator may be better positioned.

   It is in such instances that having a system for *continuing* process documentation pays off in the rapid satisfaction of needs that may arise unexpectedly. Ideally, the material should exist in organized form so as to permit knowledgeable technologists to assemble and edit a preliminary process documentation package in a matter of a few days and a full package in, say, two weeks. Of course, the transmittal of internal documents "as is" is fraught with the risk of undue disclosure, and it is best to transmit documents assembled and edited for the specific purpose at hand, a task hardly feasible if the material does not exists or exists disjointed or incomplete.

   The obvious need to avoid undue disclosure of internal issues and business methods, names, distribution lists, and the like, as well as to avoid transmitting information extraneous or strictly tangential to the technical matter at hand, must not be confused with undue reticence. If others are expected to properly implement in-house process know-how or to use it as the basis for an activity to be done on our behalf or as part of an agreement or license, the disclosure of the technical information must be no less than sufficient: what works and what does not work, the technical rationale for the prior decisions, our best understanding of the process issues, and sufficient detail of methods, process design calculations, and data. In particular, data on thermochemical safety, IH, and environmental profile need to be fully disclosed.

5. Developing the appropriate patent protection and intellectual property is also greatly facilitated by the continuing process documentation system being advocated herein. Laboratory notebooks and pilot plant log or batch sheets, while useful for assigning dates of reduction to practice, compositions of matter, procedural details, and the identification of inventors, are generally inadequate sources of cohesive process information and history.

6. Finally, there is the organizational objective of fostering a professional climate for the process technologists to thrive. The rigors and satisfactions of authorship of scientific and technical documents arising from one's own work are not to be underestimated; they contribute greatly to the individual and to the organization as a whole, even if intended for internal publication only.

> The ready access to powerful computers has created an environment in which data bases and templates or excessively formatted documents are quite seductive as a seemingly easier substitute to a system based on documents composed in clear, informative, and persuasive prose. Thus, in such tempting systems the process know-how can be thinly dispersed over an alphabet soup of spreadsheets and formlike documents that, inevitably, lack the full benefits of reflection and perspective from an author (or authors) with a process story to tell or a point of view to present as to how to implement a process. Such temptation should be resisted, as extracting useful and applicable process knowledge from the former environment is not possible without a substantial effort of retrospective composition that would have been better applied to the creation of true process documents.
>
> Scientists and engineers, usually handicapped as writers by the focus of their academic training and by misconception as to the scope of technical writing, are destined to further disadvantage if nudged by managerial convenience or by conformity into documenting their work as if filling blanks in a form or seeing the process body of knowledge as an array of dutifully filled pigeonholes.

The effort in setting down and organizing the process body of knowledge should not trail the acquisition of the raw inputs, as tardy heroic efforts to properly document accumulated knowledge are invariably not as good as the task deserves. Figure 18 outlines the body of knowledge task on the applied effort versus know-how plane.

Finally, Table 4 offers an annotated template that, if followed with sufficient discipline, carries out the various missions of the bulk drug process body

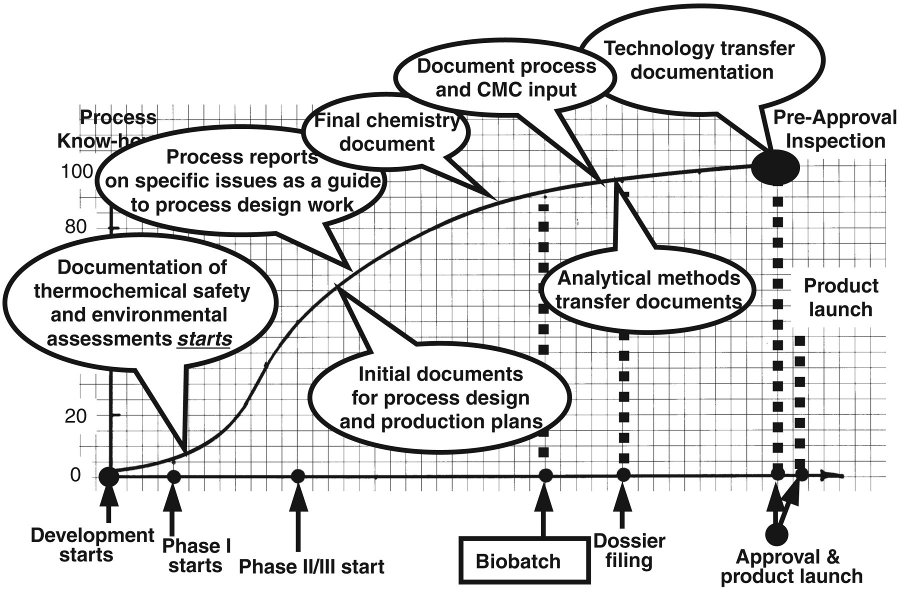

Technology transfer documentation
Document process and CMC input
Final chemistry document
Pre-Approval Inspection
Process Know-h
Process reports on specific issues as a guide to process design work
100
80
20
0
Documentation of thermochemical safety and environmental assessments *starts*
Analytical methods transfer documents
Product launch
Initial documents for process design and production plans
Development starts
Phase I starts
Phase II/III start
Biobatch
Dossier filing
Approval & product launch

FIGURE 18 The process body of knowledge in the know-how versus applied effort plane.

TABLE 4 Scope of the Process Body of Knowledge

Document	Frequency	R&D information	R&D archival	Target[a] Process design effort	Manufacturing organization	Dossier assembly
Status reports from each discipline and function	Quarterly	░	░			
Kilo lab experience	Milestone[d]	▓	░			
Pilot plant—preparative experience	Milestone[d]	▓	░		░	
Chemistry—specific reports	Milestone[d]	▓	░		░	
Microbiology—specific reports	Milestone[d]	▓	░		░	
Engineering—specific reports	Milestone[d]	▓	░	▓	░	
Analytical—specific reports	Milestone[d]	▓	░		░	
Thermochemical safety reports	Milestone[d]	░	░	▓	▓	
Environmental assessments	Milestone[d]	░	░	░	░	
Industrial hygiene matters	Milestone[d]	░	░	░	░	
Process economics	Milestone[d]	▓	░	░	▓	
Chemistry—comprehensive background	Prefiling	░	░	░	░	▓
Microbiology—comprehensive background	Prefiling	░	░	░	░	▓
Engineering—comprehensive background	Prefiling	░	░	░	░	▓

TABLE 4 Scope of the Process Body of Knowledge (*Continued*)

Document	Frequency	R&D information	R&D archival	Target[a] Process design effort	Manufacturing organization	Dossier assembly
Analytical—comprehensive background	Prefiling	▒	▒		▒	■
Environmental assessment—final	Prefiling	▒	▒	■	■	■
Stability studies	Milestoned[d]	▒	▒		▒	■
Engineering—comprehensive process document for technology transfer purposes[b]	Milestoned[d]	▒	▒	■	■	
Biobatch report	Milestoned[d]	▒	▒	▒ Summary	▒	■
Bulk drug attributes report—final	Milestoned[d]	▒	▒	■	■	
Analytical methods—final	Prefiling	▒	▒		■	■
Stability report—final	Prefiling	▒	▒		▒	■
Process demonstration document[c]	Milestone[d]	■	▒	■	■	

Notes

[a] Darker shades denote the principal targets, whereas the lighter shades denote other recipients of the document.

[b] Includes thermochemical safety and environmental. Attaches chemistry and microbiology documents as needed.

[c] Joint with the manufacturing organization.

[d] Milestone denotes that the document is generated upon certain outcomes or decision points being reached. Prefiling indicates that the document is issued *specifically* for assembly of the dossier.

of knowledge. Of particular value are the milestone reports and the specific issues reports, as they permit achieving depth and focus, while nurturing vigorous authorship by the process technologists. Such documents are invaluable as part of the comprehensive process documentation, as well as excellent raw material for the bridge documentation of the dossier. Their elaboration into external publications is usually a much lesser effort than starting from raw data and status reports. The following examples illustrate the proposed reports on milestone events and specific processing issues. Note that the titles of these reports have been composed by this author as fictitious from literature sources or approximate from his own experience with actual bulk drug process projects:

ICI 194008. The benzaldehyde imine route to the amine tosylate precursor. Bench development and readiness for scale-up (5, p. 22)
MK-787 via the ADC-6 chiral route. Results and experience from the first large-scale pilot campaign (C.B. Rosas, personal communication, 2003)
Efrotomycin. Whole broth extraction in the mixer settler and in the centrifugally aided extractor. Results and recommendations for process design at the Stonewall plant (C.B. Rosas, personal communication, 2003)
MK-401. Early environmental assessment of alternatives for the trichloro precursor (C.B. Rosas, personal communication, 2003)
MK-421. Large-scale synthesis of AlaPro in a continuous-flow system. Process design and results obtained at the large pilot scale (21)
Diazomethane. Pilot-scale generation by continuous reaction and scale-up criteria for the commercial scale (22)
LY228729. Kornfeld ketone route as the selection for scaled-up development (23)

These two kinds of reports, when added to well-designed status reports that issue regularly and not too frequently, provide the basis for a repository of a well-organized body of knowledge that can be used for the various objectives previously defined. Indeed, such reports are the core of the body of knowledge, as they gather, coalesce, and make cohesive for application the great deal of data and experience gathered during all aspects of process development.

Other aspects of the system in Table 4 are as follows:

a. All the reports and documents listed originate in the bulk drug process development area, which embraces the disciplines and function shown in Figure 12 and is part of R&D at large.
b. All process documents intended for the process design effort originate from the engineering discipline (chemical and biochemical), which embraces the thermochemical and environmental safety functions within R&D. Material from the other disciplines is attached as required.
c. All process documents intended for the dossier assembly are generated *specifically* for that purpose, usually through a chemistry, manufacturing, and control (CMC) function (as per the chemistry, manufacturing, and control component of the NDA). Such function is within the bulk drug process development area and not within regulatory affairs. This latter function should not use other process documents for its purpose of assembling the dossier or attempt to edit regular process documents on its own.
d. The biobatch, although an event taking place in the dosage form development area (and documented accordingly), will usually generate the need to document the process and related history of the bulk drug inputs used.

e. The process documentation document is generated upon completion of the technology transfer to first manufacture and is coauthored jointly by the bulk drug development area and the recipient manufacturing organizations. Chapter 3 discusses this and all other aspects of the technology transfer in some detail.

VI. NEW TRENDS AND THEIR PROBABLE IMPACT ON BULK DRUG PROCESS DEVELOPMENT

As of this writing (mid-2009), some new trends in the field of bulk drug process development seem to be taking hold on the regulatory front and on the outsourcing of first manufacture of new bulk drugs. The new outsourcing issue vis-à-vis bulk drug process development will be discussed in section "Outsourcing in Bulk Drug Process Development."

On the regulatory front, new trends have originated in the USFDA from concepts presented to the industry as opportunities to improve bulk drug manufacturing and product quality. These are now "initiatives" that seem to have become more firmly established and are creating additional regulatory expectations with apparent acquiescence by the industry.

The earlier of these initiatives is more of an umbrella thrust, launched in early 2003 under the title "Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach," proposed "to encourage the early adoption of new technological advances by the pharmaceutical industry" and a number of other improvements stemming from that broad objective (24). Two more specific initiatives spawned under the said umbrella thrust are the "Process Analytical Technology" (PAT) and the "Quality by Design" (QbD) efforts, aimed at more robust manufacturing of bulk drugs and improvement of their quality. While PAT promotes the advancement of process analytics as the means to better control bulk drug processing, QbD seeks to give a far more formal structure to the development of processes for bulk drugs.

These initiatives now seem firmly established, gaining much support, not surprisingly, from academics, suppliers of all manner of analytical and ancillary equipment, and the pharma consulting establishment. One can gauge the scope of these efforts rather directly from two publications—one academic and the other from a major pharma R&D organization. The former describes research done at the Sloan School of Management at Massachusetts Institute of Technology (MIT) (25) that is informative of the scope of PAT and QbD and gives much to read between the lines as to the potential impact of these efforts. The latter (26) describes in considerable detail the extent to which process development might become a greater task in response to a firm USFDA expectation at NDA review time. This would require considerably more effort on drug candidates (many of which will not survive as products) in a still vague quest for some just as vague incremental improvement in the quality of bulk drugs.

VII. PROCESSING RESPONSIBILITY IN BULK DRUG PROCESS DEVELOPMENT

All chemical processing (whether on a large or a small scale; for high value chemicals or commodities; or for bulk drugs, textile polymers, petrochemicals, or household products) carries a risk to those who work in the industry, to people around the manufacturing sites and beyond, and to the environment:

locally, beyond the locality, and at large. Indeed, the risk comes about from multiple directions:

1. The hazards created by the chemistry itself: (a) intended and unintended energy releases and (b) the various hazards of handling the materials involved. Bulk drugs often present a peculiar hazard; that is, the relatively high potency of the desired biological activities, as well as the collateral activities of the intermediate compounds and, of course, of the drugs themselves.
2. The specific manner in which the chemical processes are implemented at scale. Most risks in chemical processing are a function of the process design, the equipment design, and the operating procedures used to manufacture the products. In other words, *the same inherent hazard can be implemented at various levels of risk, depending on the specifics of implementation*, and often enough details matter.

Hazard: a source of danger, of possible injury or loss

Risk: the probability of suffering a given loss or injury from a hazard

3. The local context in which the manufacturing process is implemented. First, there are factors, such as the proximity to populated areas, the direct impact on sensitive receiving bodies of water or other valuable habitats, and a less apparent impact on remote parts of the environment at large. Then, as a lesser subset of those risks are the various statutory and regulatory constraints that create liability potentials or that may impede timely manufacture if not properly addressed.

> It is one of the prime responsibilities of the bulk drug process development organization to seek processes of acceptable levels of hazard in both the chemistry and its engineering and to participate in the process design and manufacturing plans to see to it that their implementation risk is sufficiently low. Of all aspects of technology transfer, none demands more in terms of the development team thrusting itself downstream and seeking the closest collaboration with the manufacturing organization. Clearly, the greatest opportunity for success exists at the developmental stage of the R&D process work, when the process is conceived and developed; engineering low risk into the implementation of a hazardous process is always the second choice for the bulk drug process development team and the collaborating process design function. For example, much safer process alternatives seemed to exist for the process that led to the 1974 catastrophe in Bhopal, India (27); one called for a different chemical route and the other for a different process design of the original chemistry.
>
> Incidents such as Seveso, Italy, 1976 (27, 28), and Bhopal illustrate the potential for catastrophic events from aberrant chemical processing and design, sloppy operating practices, and incomplete knowledge about probable unintended events and consequences.

Generally useful practices in this aspect of bulk drug process development are as follows:

Early assessment to guide the process conception and choices. This implies availability within the process development organization of, or facile access to, laboratory capabilities to evaluate thermochemical and environmental hazards. The evaluation of industrial hygiene (IH) hazards is aimed at the protection of personnel and is facilitated by the availability or access to adequate toxicology resources such as those generally available to a research drug firm. This IH context, however, differs substantially from that of evaluating the risk to patients taking the drugs, and a different subset of skills and methods applies.

Continuing assessment as the process develops, including a vigorous interaction with the process design function and the manufacturing organization. For example, issues such as the choice of manufacturing site, which influences the risk, cannot be settled by the process development team alone, nor can they be properly settled without the hazards assessed during development.

Reasonably early decision on the in-house versus outside manufacturing choices, as the latter requires technology transfer and due diligence work, as well as the inevitably longer cycle for reaching the necessary technical and business agreements (more on this in section "Processing Responsibility in Bulk Drug Process Development").

A. Thermochemical Process Safety

Most chemical processing operations have energy exchanges between process streams and the surroundings; process streams are heated or cooled for various purposes, and such exchanges need to be safe. Heated streams must not exceed limits that generate undue pressures or undesired chemical events, whereas cooled streams must not freeze and interrupt process flows, or hamper a desired chemical reaction and accumulate unstable intermediates.

> A distinction needs to be made between limits observed to maintain process performance and limits observed to avoid a hazardous operating condition. The preceding paragraph refers, of course, to the latter limits, as depicted in Figure 19 using the safe processing envelope concept.

The thermochemical safety of chemical processing deals with the safe handling of the energy released from chemical reactions and with the prevention of unwanted releases of energy. Chemical reactants may, when converted to products, result in the transformation of chemical energy into heat, and during such exothermic reactions the heat release needs to be safely managed. In addition, chemical process streams may reach abnormal conditions that cause

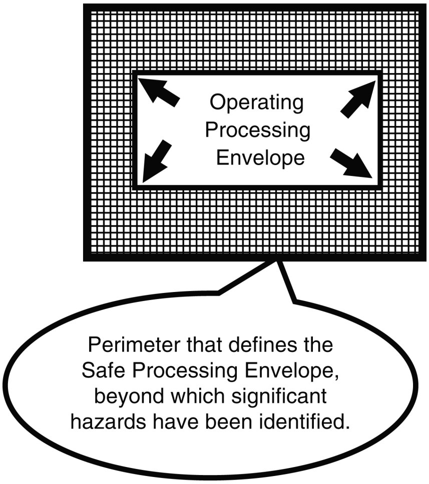

Operating
Processing
Envelope
Perimeter that defines the Safe Processing Envelope, beyond which significant hazards have been identified.

FIGURE 19 Processing limits for performance and for safety. Processing limits define the perimeter of the operating envelope that results in the range of desired process performance, whereas the safety limits define the safe processing envelope perimeter, given the identified hazards that lie beyond. For example, a distillation is to be carried out at 90–100°C, whereas the high-temperature interlock that shuts off the steam is set at 125°C because a significant exotherm initiates at 160°C.

unintended exothermic reactions, with the attendant formation of unintended by-products and release of energy.

Hence the objectives of thermochemical process safety as a distinct principal component of processing safety at large are as follows:

Identify all *intended* energy releases and determine their magnitude, rates, and by-product releases, such as gas evolution and their composition. These determinations need to be made over the appropriate range of process conditions.

Identify *unintended* chemical events and energy releases for *reasonable* hypothetical situations (e.g., excess temperature by loss of coolant or runaway, excessive evaporation of solvent, and interrupted reaction cycle) and assess their magnitude, probable rate, and consequences with respect to containment, gas evolution, and, when indicated, the composition and toxicity of the components of a plausible release.

Identify and quantify the hazards of handling the process streams and materials with respect to shock sensitivity, flammability, explosiveness in air mixtures, dust/air explosiveness, etc.

Seek process development solutions to avoid or reduce hazards. For example, one might seek an alternative reactant, a reaction medium that permits a lower reaction temperature or, in the ultimate, a different synthesis scheme for the conversions at hand.

Provide process design solutions to those hazards that cannot be reasonably developed out of the process, thus reducing their risk to levels appropriately low for the operating context. For example, a hazardous nitration reaction may be implemented in a reactor system that does not use aqueous coolants or that is equipped with a suitable quenching vessel, a sufficient containment system, or a continuous tubular reactor with large cooling surfaces and a small volume of reactive in-process materials. Similarly, a process or portions of a process with a hazard of explosion is preferably operated in a plant site that is distant from populated areas (vs. an otherwise more suitable plant site not as distant from populated areas), or a process with an identified hazard of aquatic toxicity in its untreated waste would not be operated in a plant site that normally discharges to an aquatic habitat. In both cases one will take preventive measures to reduce the risk, but a risk differential will exist between the two plant sites.

> From the above, and most importantly, *the practice of thermochemical safety far transcends the evaluation or the assessment of hazards*. It also demands that skillful solutions to the hazards be provided so as to eliminate them or reduce their risks, as required. While the reader may view this statement as redundant or exceedingly tutorial, the fact is that a functional discontinuity between the assessment of thermochemical process hazards and the implementation of the process frequently exists, creating an ever-present pitfall for the unwary, the sloppy, the overwhelmed, and the unqualified, and even organizations with the requisite critical mass of skills and well-documented procedures need to be vigilant to the gap. As in most other aspects of bulk drug process development, the utmost integration of process development and process design is the best approach to thermochemical process safety, organizational divides notwithstanding.
>
> Additionally, the above reflects the fact that the same hazard (e.g., a reaction mass that can decompose explosively upon total loss of solvent) poses a different risk according to the context of implementation. Thus, for the example just given of a major hazard, a process design based on the operator's attentiveness and simple process controls would entail a greater risk than a design based on interlocking and

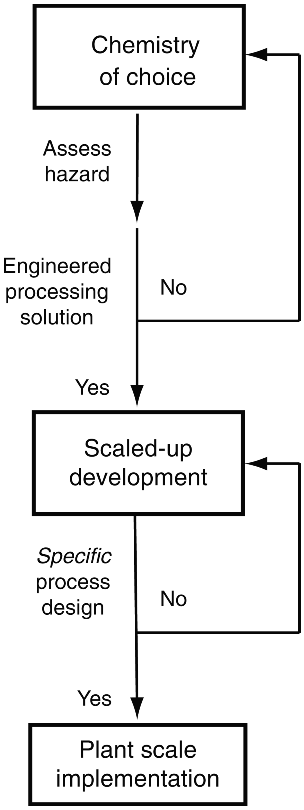

Chemistry of choice
Assess hazard
Engineered processing solution
No
Yes
Scaled-up development
Specific process design
No
Yes
Plant scale implementation

FIGURE 20 Thermochemical process safety in bulk drug process development.

redundant measures to prevent total loss of solvent as well as the operator's attentiveness. To wit, the operational risk arising from a process hazard is very much a function of the specifics of the operational context.

There are, of course, many other aspects of processing safety that are unrelated to, or overlap with, thermochemical process safety. Among the overlapping, fire and explosion hazards due to flammables handling stand out, whereas the unrelated (e.g., falls, burns, asphyxiation in enclosed spaces, and static electricity) are generally addressed through the aggregate of well-established measures of operational safety, facility design, insurance policy expectations, and applicable industrial or building codes.

It seems best, even for the introductory scope of this chapter, that before approaching a more specific discussion of the fundamentals and the practice of thermochemical process safety, the presentation of a broad perspective be attempted—hence Figure 20, in which the field is viewed from a sufficiently high vantage and that the reader is urged to examine in earnest before going further.

Three key points arise from Figure 20:

The chemistry defines the overall scope of the hazards: the energy release potential of the reactants and other materials used, the energy release potential of the reaction and process streams generated, and the toxicity hazard that attends to all the compounds involved, whether inputs, intended, or generated by aberration. Accordingly, chemical acumen is utmost in the assessment and follow-up of the hazards defined by the structures at hand.

Upon assessment, a broader set of skills is needed. Will the hazard be avoided altogether by a change in the chemistry, or will its risk be sufficiently reduced by a process solution? Either approach requires engineering acumen to determine that a process solution is not advisable or probable or to devise a suitable alternative.

Finally, the implementation of whatever process is arrived at through development, and its indispensable process design collaboration, must go through further engineering analysis by which all the applicable considerations must be pursued to the requisite level of detail: from the sizing of vessel relief and area explosion venting on the basis of thermochemical and related data to the evaluation of risk scenarios that will dictate the necessary margins of safety relative to overlapping safety, site specifics (e.g., weather precedents, proximity to people or valuable environments, applicable regulations, insurance policy expectations), and all the way up to the probable perceptions in the neighboring communities.

Prior to the catastrophes in Seveso in 1976 (24,25) and in Bhopal in 1984 (24), these admonitions would have seem unwarranted and even melodramatic; but not any more. Finally, seeking relief in the small scale of bulk drug chemical processing does not help, as both instances of chemical processing operations gone badly awry were of small or modest scale.

1. *Hazard Assessment and Methods in Thermochemical Process Safety*

Thermochemical hazards are numerous and richly varied in kind, each requiring more than passing consideration and, if appropriate, an assessment by engineering design calculations and simulation, experimentation, or both. The task calls for experienced good judgment, as the possibilities are too numerous. For example, an organic synthesis of six distinct steps, with up to, say, ten distinct intermediate structures generated, might also have a total of forty different material inputs and process streams. Experimental assessment of each is a large burden that, invariably, can be greatly reduced by the said experienced good judgment.

Herein there is not, of course, the aim to comprehensively present this subject. Indeed, the literature is ample (not surprisingly, most was written after the 1976–1984 experiences), and the serious reader is earnestly referred to various references, preferably in the listed sequence (24, 26, 27, 28). Clearly, this is not work for the dilettanti but for professionals willing to invest in acquiring and applying focused know-how in a multidisciplinary environment; too much is at stake. Similarly, firms engaged in bulk drug processing cannot approach the work in half measures or contract it out indiscriminately or unaware of the pitfalls of doing so.

Let us discuss another perspective, this time from a closer vantage—that of the thermochemical hazards assessment. First, as indicated earlier, the structures at hand provide very useful leads as to what to expect. As a good rule of thumb, organic compounds that are rich in nitrogen, oxygen, or both are high on the list of reactivity and energy release structures, followed by some specific bonds and then by the less obvious cases that exist in organic synthesis, albeit less frequently (29, pp. 18–28; 30, pp. 28–52; 31, pp. 22–27). Once so alerted, the hazards assessor has a good number of techniques for estimation of heats of reaction, for rapid screening of exotherms and instabilities in materials, compounds and process streams, for accurate calorimetry work under close to actual process conditions, and for very specific follow-up of hazardous conditions (30, pp. 1–28 and 52–88; 31, pp. 27–45). Indeed, the techniques are so numerous that care must be taken to walk the fine line between necessary and marginal testing, striving to reserve the more elaborate and exhaustive methods for the cases that merit them. For example, the thermal stability of process materials and streams can be pursued to great lengths (32), as required. Similarly, the subsequent hazards of vapor or gas release or toxicity of the released materials need to be pursued with similar acuity, as one may go too far as easily as not far enough. In this, the incisiveness of the screening effort makes the difference.

The well-executed hazards assessment meets its three basic objectives: (a) identifying and quantifying the heat effects of the intended chemistry, (b) identifying and quantifying, albeit not always as precisely, the thermochemical energy hazards from aberrant conditions, and (c) identifying and quantifying those hazards associated with the handling of process materials and their instabilities. Again, it is work with a great many nuances for which chemical, physicochemical, and engineering acumens are indispensable.

> By way of vivid illustration of these assertions, one might consider the following instance in which a labile nitrogen-rich compound was isolated as a water-moist powdery solid and dried under vacuum at ~50°C. These latter drying conditions had been set at ~50°C away from the rapid and large exothermic decomposition of the compound, found to initiate at ~100°C in the screening work. Additionally, the heating medium used in the drying step was limited to ~55°C, and an ample vacuum capacity and a suitably low terminal pressure provided for the thorough removal of water. After months of processing at the ton scale, a process change was introduced in the isolation, substituting a mineral acid for another in the final acidification prior to filtration and washing. This seemingly innocuous change resulted in a product of slightly lesser purity that, alas, was significantly less stable. The latter fact came forward upon violent decomposition of ~ one ton of product during the drying step. Subsequent investigation revealed that the process change product was somewhat less crystalline and had a significantly earlier onset of decomposition, such that at 50°C to 55°C, the self-heating process of decomposition started and rapidly took the material to its violent decomposition.

Finally, thermochemical hazards assessment needs to start upon scale-up to the kilo lab, and if the structures at hand are suspect, some basic screening should be done even sooner. The effort then needs to continue as the process is developed and scaled up to the pilot plant, ensuring that significant process changes are not missed—a task of skillful vigilance, as the previous example emphasizes.

2. *Process Design from the Assessed Hazards and Achieving an Acceptable Risk*

As indicated in Figure 20, the hazards assessment data need to be placed in a process design context in which scale issues arise forcibly: loss of surface to volume ratio, longer time cycles of certain batch events, more difficult mixing, larger in-process inventories, and many other. Upon scaled-up development, a reasonably specific design of the scaled-up operation needs to be challenged by the hazard and the resulting level of risk evaluated. This requires a sufficient engineering input and a deliberation commensurate with the magnitude of the hazard, and the exercise resembles the do-loops of computational code, with the effort resulting in a process design solution deemed to have an acceptable risk. Often enough this analysis leads to (a) a significant change in the basic process (the scaled-up risk demands a lesser hazard) or (b) a highly engineered design (the hazard is accepted, but its scaled-up risk is also accepted). Examples of these outcomes are the switch to a different reaction to get to the same structure or the use of a continuous reactor (or skipping the isolation of a dry unstable intermediate), respectively.

Beyond the above, more detailed methods of analysis exist for final plant design [e.g., hazardous operations review methods (HAZOPS) or similar methods] (33, pp. 42–178), with the objective of ferreting out the risks arising from the basic process hazards as well as all other overlapping hazards in the specific context for the process operation. In many cases, the specific risk analysis results in changes to the safe processing envelope so as to deal effectively with the risks. This result is depicted in Figure 21, where a contoured envelope is adopted so as to place greater "distance" between the permissible range of process variables and the risks. For example, the mixed acid concentration in a hazardous nitration may be lowered to significantly reduce the risk of catastrophic failure by corrosion of the preferred (and existing) reactor vessel in the plant.

Eventually, this continuing exercise embraces all the issues of the context of choice: the intended production capacity, the intended operating space, the plant site location, and their myriad specifics. This is one of the principal reasons for having a close collaboration between the bulk drug development function and the process design function. The latter will usually be the most direct conduit to other functions at play, such as production planning, operational safety, and environmental compliance. This desirable collaboration, however, does not imply that the bulk drug development team is a lesser participant in the process design effort; far from it, in the optimal scenario the

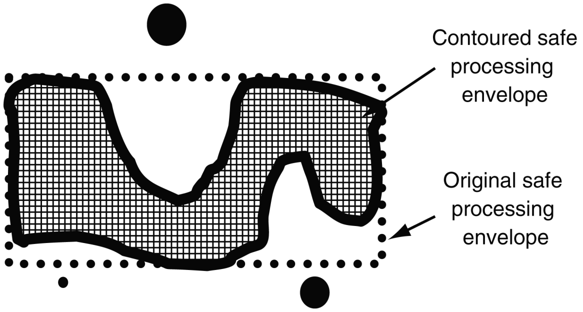

Contoured safe processing envelope
Original safe processing envelope

FIGURE 21 The contoured safe processing envelope. Detailed analysis of hazards in a specific context (specific process and plant designs) usually reveals specific risks, and implementation of the process in that context may require that the original safe processing envelope be contoured (i.e., modified for the said risks). In the figure, the original envelope has been shaped so as to create a distance from the risks that bears proportion to the magnitude of the risk, which is depicted by the size of each circular symbol for the risk.

bulk drug development function possesses (and nurtures) sufficient process design skills.

3. Thermochemical Process Safety in Technology Transfer

By the time that formal technology transfer takes place, the thermochemical process safety issues are largely settled in the first manufacturing context, as described in the preceding paragraph. All that remains is the confirmation of the process performance and a reassessment of the risk on the basis of actual operating experience in the commercial plant. Of particular interest is how well the thermochemical process safety measures have been dovetailed with the full set of operational and environmental safety needs at the plant site, as this latter set, while preoccupied with a very broad range of hazards requiring very detailed measures (e.g., the lighting of exit signs, painting of yellow strips, explosion-proofing of electrical equipment, and inertion of vessels with flammable materials), overlaps with thermochemical process safety (and depends on the hazards assessment data) on issues such as relief venting for runaway reactions, the lesser risk location of hazardous processing, emergency planning for chemical releases, etc.

B. Industrial Hygiene

Examples of serious harm to workers from materials used and made in the manufacturing workplace are well known: black lung disease and asbestosis stand out by the number of people affected and the severity of the results by long-term exposure to coal dust and asbestos fibers, respectively. Thus it is logical that, when dealing with bulk drugs (chemicals with potent and multiple biological activities), and as with thermochemical process safety, IH issues arise early in the bulk drug process development cycle.

Unlike thermochemical process safety, however, the bulk of the IH effort (its hazards assessment and risk analysis) falls elsewhere, as the toxicology and preventive measure skills are not in the bulk drug process development function at all. Nevertheless, the bulk drug development function does have some important roles to play in ensuring the IH safety of its processes.

One of these roles is to be very alert to what chemicals are used (and their specific forms' physicochemical properties) and ensure that the requisite toxicology screening is done on a timely basis, as well as track relevant process changes during development for their appropriate IH assessment. If anything, the bulk drug development team is very well positioned to be sensitive to the IH issues of new drug candidates, given its knowledge of their biological activities and, at the very least, of their in vitro potencies. The interaction with the toxicology function also provides an early exposure to the toxicological profile of the bulk drug as it develops. Thus, if a compound's intended use is based on its cytotoxicity, that sets the stage for its handling even at the small bench scale. Indeed, there are toxicology screens that apply to the IH measures, since the latter are concerned not only with the bulk drug proper but with all materials handled during the preparation or manufacture of the bulk drug. In many cases, intermediate compounds are found to have undesirable markers in these screens, for example, dermal or ocular irritants, assorted acute toxicities, and potential teratogenicity or mutagenicity. The inevitable focus on the toxicology of the bulk drug must be balanced by ensuring the proper examination of the intermediates and to do so at an early stage. It is not possible, as an operating premise, to treat all compounds as worst cases; appropriate data are needed for the protection of the personnel during development and for setting up the proper engineering measures and procedures for first manufacture.

The other role of the bulk drug team is, of course, to engineer major IH challenges out of the process, not unlike the elimination of thermochemical process hazards. For example, the process development effort may seek the avoidance of isolation of specific intermediates or of their handling as dry solids. One might seek their fine-particle distributions enlarged, and with the bulk drug proper, crystallization technology may be used to avoid milling of solids. Additionally, technologies of containment have been developed to deal with compounds of high potency in their biological activities at any scale of processing, and such technologies need to be practiced in the well-rounded bulk drug pilot plant, as indicated in Table 3.

Finally, access to sufficient IH skills is needed by the bulk drug process development function. Many IH issues are not in the scope of the toxicology function of drug development and require an additional set of skills overlapping with operational safety and occupational health regulations as well. In one instance, a seemingly adequate containment of fumes and ventilation in an area where phosphorus pentachloride was handled could not prevent a very mild baseline irritation of respiratory mucosa of workers such that, upon their subsequent handling of a penicillin derivative in the next production campaign, severe allergic reactions developed. Nevertheless, the practitioner of bulk drug process development should be more than just aware of the IH issues and is hereby referred to some suitable introductory material (27, pp. 22–81).

C. Environmental Safety

Here we return to a forceful and decisive role of the bulk drug process development team. Just as the chemistry sets the scope of the thermochemical process hazards, it also sets the environmental profile of a bulk drug process: its inherent benevolence (*green chemistry*) as one extreme and its highly engineered implementation, made possible by intensive and extensive abatement and waste treatment measures, as the other extreme.

Early assessment of environmental profile (or potential impact) is the best tool to steer the chemistry along a greener path. While the actual data are much harder to obtain for some key components of the profile (e.g., aquatic toxicity), suitable screens exist (34, pp. 93–177; 35). These, coupled with preliminary process design as to waste loads and some assumptions as to manufacturing sites, make it possible to feed back to the synthesis conception any of the following:

The profile is such so as to merit the immediate search for alternatives for some specific aspects of the synthesis. The synthesis team may find such urging very disagreeable, but organic chemists have come a long way in accepting such judgments, even as early estimates. Of course, much depends on the level of skill and recognition of the assessors, which is one of the reasons for the early environmental assessment effort to be carried out by qualified people within the process development function, where they are generally perceived as less bureaucratic and regulation driven than comparably qualified people in a corporate or manufacturing function.

The profile is promising, and some particular aspects need adjustment or early environmental engineering attention.

Following the early assessment, the parallel with the thermochemical process safety effort is quite close, except for the greater difficulty and longer time cycle of some of the key data gathering. The issue of risk as a function of context, site location in particular, arises more sharply than with thermochemical risks due to the greater variety of downstream impact issues and of how far downstream they might arise. Questions of impact of the eventual discharges on seemingly remote and valuable habitats can arise, particularly with residual concentrations of highly potent drugs (e.g., mutagens and endocrine modifiers). More recently, the issues of drugs in drinking water sources and the ultimate fate of drugs excreted by patients have entered the regulatory expectations.

The companion chapter 3 will revisit the environmental safety topic in the process design and technology transfer context. However, it can be stated herein that the environmental profile of the bulk drug process has moved up in the priorities of R&D, as the drug dossier needs to address various levels of environmental safety assurances in individual regulatory submissions. The NDA in the United States, for example, requires an environmental impact statement of a scope that cannot be dismissed. It no longer suffices to provide statements of assurance as to compliance with all applicable environmental regulations.

Finally, there often are overlapping jurisdictions bearing on the ability of getting first manufacture started on a timely basis. All need to be satisfied that the intended manufacturing will not adversely affect the respective environments, just as communities and environmental advocacy organizations may need to be reassured. For all these and the above reasons, the environmental profile of the bulk drug process has risen in its importance, making it a good business choice to have a competent and well-equipped environmental technology function within the bulk drug development function and a close collaboration with the complementary environmental skills in the manufacturing and corporate organizations.

VIII. OUTSOURCING IN BULK DRUG PROCESS DEVELOPMENT

The last decade has seen a drastic transformation of the bulk drug manufacturing milieu, including the adoption by the research-based drug industry of a business model (perhaps approached as a gospel in some cases) that greatly reduces the role of bulk drug manufacturing in-house and increasingly places it with outside suppliers. The latter proliferated in the rush to capture a more profitable business of fine and specialty chemicals, and many were fully engaged in drug intermediates and bulk drug manufacturing to the point that by 2002–2004 overcapacity existed. Since then, however, pharma has made an even greater commitment to the outsourcing business models, further weakening its bulk drug manufacturing stance and capabilities. As the manufacturing scope is decreased, the impact on the process development capabilities seems inevitable, as more of the process development effort drifts to the suppliers and the scope of the technology transfer task—vital nourishment to process development skills—decreases.

Inevitably, this has had a major impact on the bulk drug process development as well. Given the manufacturing driver for this shift, the overall outsourcing topic will be discussed in the next chapter, including the said impact on the bulk process development.

IX. IN CLOSING

Clearly, this chapter has described bulk drug process development as a complex, richly textured activity that is deeply rooted in scientific and engineering skill. The discussion has been largely based in the context of a large drug company where all the requisite skills reside mostly in R&D but are complemented well by those of the downstream organizations.

The reader may well ask, particularly as the new drug business faces increased pressures to do it faster and in a more regulated environment, does the smaller organization have a chance to succeed? What if the seemingly indispensable critical mass is not there and, instead, the task must be done by dovetailing as best one can resources and functions from multiple organizations? To the author the answer is clear. Bulk drug process development is a business where size matters and matters greatly, and if success is measured by the timely introduction of new drugs (not just one drug at a time) on a broad marketing base, then the smaller organizations labor at a disadvantage and the virtual company struggles with projects of any scope. Indeed, for bulk drug projects of unusual technical difficulty, the smaller organization seems faced with insuperable odds. Yet, none of this denies the opportunity for the bulk drug process developer practitioner to excel and find professional fulfillment in any environment without regard to size; all that is needed is the requisite skill and dedication to one's work, as well as reaching out for the best possible collaborations that might be available.

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3

Bulk Drugs: Process Design, Technology Transfer, and First Manufacture

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I. INTRODUCTION

This chapter complements its preceding companion chapter 2, which addressed the task of bulk drug process development. The tasks addressed herein overlap the development of the process, as process design does, or culminate the development task, as technology transfer and first manufacture do. As in the previous chapter, this one seeks to provide a sound perspective of the latter tasks to the uninitiated and the new practitioner, while the structured presentation and the deliberately inserted points of view may interest and possibly challenge the experienced practitioner.

First, there is the promotion of deliberately overlapping the experimental development of the process with its design into a manufacturing plant. Valuable as it is, however, this overlap is often not used as a powerful method in seeking the better process and a manufacturing plant to match, but is practiced ineffectively, strictly as a necessity of the time-to-market imperative. Sometimes the jurisdictional divide at the development-design boundary is too deep; or there is an interdisciplinary gap, with chemists on one side and engineers on the other; or the process design becomes earnest too late to influence the development. Indeed, many scale-up difficulties cannot be identified or quantified soon enough without a sufficient process design effort that runs parallel and close to the development.

Then, there is the lessened character that the process design subdiscipline has developed as a result of many bulk drug projects being handled by design and construction firms, where the practice of process design can be unduly conservative, or too pliant to the client's wishes, or so lacking in the bulk drug processing skills so as to offer nothing beyond what the client brings to the project, with the client's errors or limitations dutifully incorporated into the design. In other projects, such as those that outsource manufacturing, the emphasis on process retrofit into an existing plant is heavy and the process design, if any, is often beyond the grasp of the client. This harsh assessment is warranted by the penalties often paid, unknowingly at the time, because of the lack of the appropriate process design skills and practices in scaling up bulk drug processes, or simply by the absence of a mechanism to exploit the opportunities in deliberately overlapping process development and design.

Alas, chemical process design skills are hardly ever taught formally; the first and last academic exposure most engineering students have to the subject is a rather superficial and highly structured "process design" project at the undergraduate level. To make matters worse, computer software tools that can aid process design have usurped that undergraduate task, often reducing the student's effort to little more than filling blanks in fairly rigid templates, sometimes with proposed operational designs that can be hilarious (e.g., a *stirred* tank for a Kolbe reaction loaded with 4000 kg of 2-in. steel balls!) and usually missing the learning experience of manipulating design options at the conceptual level. Yet, sound process design is a requisite of good process performance in the manufacturing plant, and creative process design is practically indispensable in achieving superior processes and plants, as well as in exploiting advantageous chemistry that might be difficult to implement in the plant. Thus the wisdom of fostering the formal development of those skills and the development-design overlap in industrial practice, placing emphasis on the conceptual and unstructured aspects, as these are not addressed well by the current computational aids that are widely used and are less likely to be pursued aggressively by engineering design contractors.

Another objective of this chapter is to establish the value of another overlap: process design is, for all practical purposes, the first stage of technology transfer. Moving a bulk drug process from the development environment to that of first manufacture is a delicate task that is made more difficult without a competent process design component. Once these arguments are presented, this chapter is meant to flow rather naturally as a series of annotated commonsense prescriptions for sound technology transfer, proven to the author over numerous projects and observations that ranged wide through the practice of bulk drug chemical processing. We will dwell on these measures as they apply through first manufacture, setting the stage for mature manufacture as a function of product growth.

This chapter also includes, in closing, some observations on the technologies of bulk drug processing—development as well as manufacture. While perhaps couched as pearls of wisdom, they reflect some of the deeply held views of the author that could help the new practitioner with a perspective of the bulk drug business enterprise.

II. THE PROCESS DESIGN TASK IN BULK DRUGS

A. Definition and Scope of Process Design

Process design is, first of all, *not* the development of precise specifications for a performing chemical plant, whether built on a green field, or merely the modification of an existing facility to accept a new process. Instead, process design takes place well before such specifications can be drawn, and it is only through its completion that the *plant design* (in contrast to the process design) can be carried out, defining the future plant to the extent that equipment can be procured and installed or an existing plant modified. Necessarily, process design has a much broader scope, including a largely conceptual component that comes about early in the overall effort, confronting issues and unknowns in a sequence that is outlined in the following sets of questions:

1. Broad-brush definition of the task and its probable capital cost, venues, and timetable.
    - At what approximate output will the process be first run and when? On what operating basis?
    - What manufacturing cost can we project? What are the top cost reduction targets?
    - What are the probable materials and energy balances of the process?
    - Which operating site makes the most sense? In what operating area of the site of choice?

- Should it be run in a new plant or a retrofit?
- What are the prospects for outsourcing some or all of the manufacturing task? Which tasks are most likely to be outsourced? When will that decision be made?
- What is the probable range of capital cost? Is the high end of the range acceptable? Is the low end (via outsourcing) attractive enough?
- What is the probable timetable to an operational plant? Is the timetable acceptable?

Starting with these and other broad questions discussed earlier, the process design should continue *without pause* as the features of the process take shape with the benefit of feedback, and the issues of site selection and outsourcing become more distinct. Indeed, as Figure 1 illustrates, the fundamental objective of the parallel exercise with development is for the latter to reflect the teachings of the process design.

2. Definition of the various process steps as they might be operated in the most probable venue of choice. For example:
    - Will the process run as currently operated at the pilot scale? At what scale? Batchwise? Continuously?
    - Integrated for optimal layout or placed opportunistically throughout the existing plant?

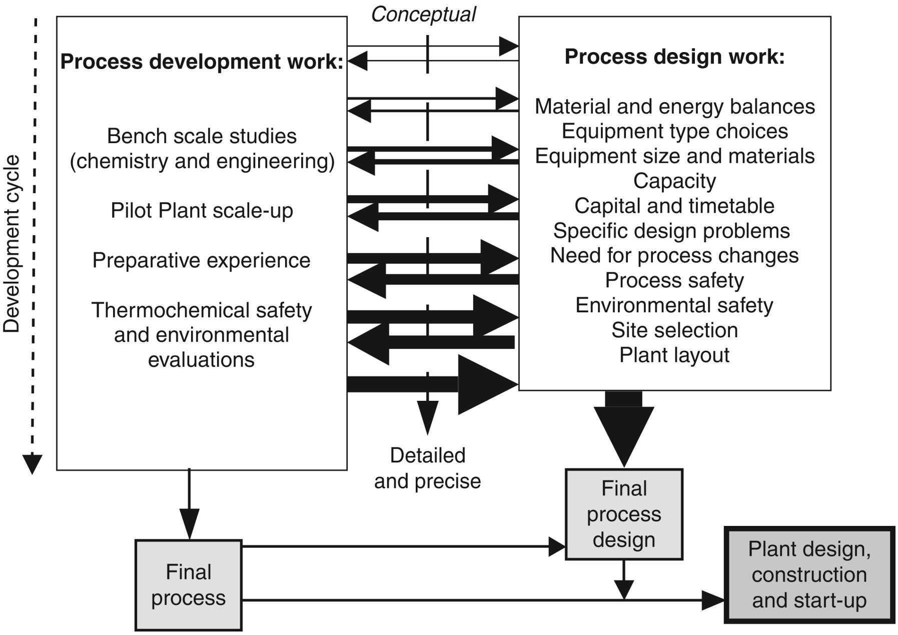

Conceptual
Process development work:
Bench scale studies (chemistry and engineering)
Pilot Plant scale-up
Preparative experience
Thermochemical safety and environmental evaluations
Development cycle
Process design work:
Material and energy balances
Equipment type choices
Equipment size and materials
Capacity
Capital and timetable
Specific design problems
Need for process changes
Process safety
Environmental safety
Site selection
Plant layout
Detailed and precise
Final process design
Final process
Plant design, construction and start-up

FIGURE 1 Flow chart of the process design effort—Bulk drugs. The overlap with the process development effort provides an unmatched opportunity to seek the better process by using the feedback that process design can provide. Both efforts move from the conceptual to the detailed and precise that is eventually needed to permit plant design, construction, and start-up. Similarly, as indicated by the horizontal arrows between the two efforts, both feedforward and feedback improve in defining the evolving process and its design as the efforts take place.

- With or without solvent recovery or recycle?
- Are the environmental burdens acceptable?
- Are there waste or pollution issues demanding at-source treatment?
- What are the identifiable risks from the know process hazards? Where are the safe processing boundaries (i.e., the safe processing envelope described in Fig. 19 of chap. 2)?
- First flow sheets and their material and energy balances are defined. What adjustments do they suggest? To the design or to the process?

3. More specific design issues arise. For example:
   - How will these solids be separated from the highly viscous process stream? The pilot scale practice has been an expedient not practical at the manufacturing scale.
   - How will this large exothermic reaction be handled within the residence time constraints?
   - How will this aberrant and unintended exotherm be precluded? Or the associated risk reduced?
   - The current method of isolation requires unprecedented adsorption column diameters. Shall we seek alternatives? Or should we carry out more scale-up studies?
   - Is this solvent throughput reasonable? Can concentrations be adjusted? Or should we use an internal recycle loop via flash evaporation?
   - Drying these particular solids seems intractable at the plant scale. Can we move the wet solids forward? Use a more volatile solvent wash to facilitate the drying?
   - Availability of a vessel in the required material of construction is a problem. Do we seek alternative materials or alternative processing conditions?
   - The industrial hygiene data for this intermediate demands a given level of containment. Can the isolation be avoided?

Clearly, a myriad of such questions arise, *preferably sooner rather than later*. There will not be satisfactory answers to some, which should trigger subsequent iterations in the feedback loop shown in Figure 1. Although some extent of feedback from manufacturing planning always occurs, it is best by far to establish the feedback loop as early as possible and in a framework that makes the process development effort sensitive to it. In other words, there must be responsiveness within the development effort, as indicated in Figure 1, particularly when the issues that arise are inconvenient or undermine the more basic process choices that might have been made or that have the greatest appeal to the development team.

The best conditions exist where there is a process design capability that collaborates with the process development team; indeed, the latter should participate by virtue of having a modicum of skills to understand the process design feedback, as well as having the wisdom to act as needed. Conversely, the process design team must have sufficient knowledge of chemical processing at large to understand the process imperatives or the rationale that makes a given process approach so attractive as to accept the design challenges. Frequent communication, even if at times burdensome, and overlapping efforts are the key components of successful process design for a developing process. A new process, even if presented as developed, must survive the challenge of its

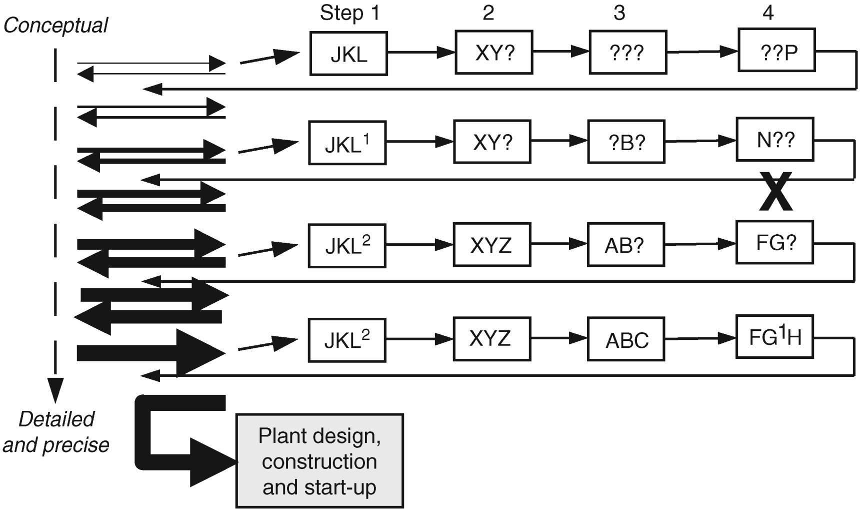


FIGURE 2 Process design of a developing bulk drug process. Along the same lines of Figure 1, process approaches (chemistry included) are indicated by the first letter in each box, versions within the approach are indicated by the subsequent letters, and elaborations of a version by the superscripts, all used to depict the optimal evolution of a process through the continuous feed-forward and feedback between development and process design. Note that Step 1 moved forward with little change, whereas in Step 4 a completely different process approach was found necessary.

process design, thus the compelling rationale for the overlap of the two tasks, as shown in Figure 1. Another depiction of the results of the overlap of process development and design is given in Figure 2, an example of a multistep process under development, showing the range of what happens as process design takes place: from straightforward implementation (Step 1) to iterative effort requiring change of the process concepts (Step 4) as indicated by the use of different letters and superscripts.

After considerable evolution, the principal finished product of process design is the process and instrumentation diagram (P&ID), eventually issued in what is usually called the approved-for-construction (AFC) version, the definitive successor of various intermediate versions and their revisions. A slice of such a P&ID is shown, with some simplifications, in Figure 3. Obviously, there is a great deal of supporting detail that attaches to the P&ID AFC, but a critical examination of the diagram is the core of the subsequent plant design effort.

Perhaps the most difficult aspect of overlapping the development and design for a chemical process in flux is that of the uncertainties from unsettled process issues, which may range, depending on the character of the process development organization, up to the actual chemistry for part of the process. These uncertainties often appear in the P&ID as blank or ill-defined areas under the heading "To Be Determined," as depicted in Figure 4. Such uncertainties arise in the projects with the most technical difficulty or in the fortunate instances when a clearly superior and compelling part of the process exists but comes late to the fore, thus presenting the most severe test to the skill and discipline of the development-design interaction. Organizations or interacting

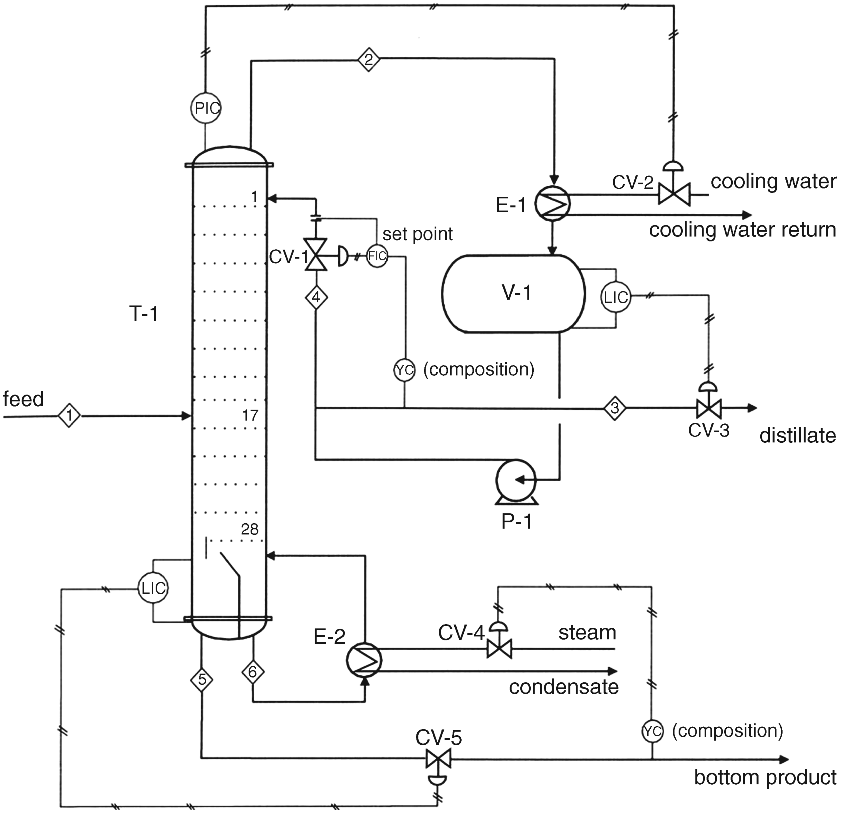

PIC
2
cooling water
CV-2
E-1
cooling water return
1
set point
CV-1
FIC
4
V-1
LIC
T-1
YC (composition)
feed
1
17
3
CV-3
distillate
P-1
28
LIC
E-2
CV-4
steam
condensate
5
6
CV-5
YC (composition)
bottom product

FIGURE 3 The process and instrumentation diagram (P&ID). Shown as a simplified version stripped of some detail (to permit an uncluttered and legible diagram for reproduction herein), the P&ID identifies each item of processing equipment, their connectivity, and the control instrumentation loops. Not shown, but generally present in the final AFC version of the P&ID are the details of the piping, materials of construction, pump capacities, etc. Obviously, there is a wealth of other material that accompanies the P&ID, but the latter is the centerpiece of the process design package used to execute the plant design. *Source*: From Ref. 1.

teams that can manage those situations under the time-to-market compulsion have a major tactical advantage, and if they can exploit them under an enlightened R&D management, their advantage can be strategic.

There is, of course, the plant design effort, requiring a level of detail that far exceeds that of process design and that follows it with considerable overlap, as depicted in Figure 5. We should note herein that a bad process design cannot be turned into a good one by plant design means, as the latter are aimed at faithful implementation of the process design intent.

Finally, it should be understood that the discipline explicit in the above prescriptions does not depend all that much on the size of the organization; it can be applied by the smallest team as long as the requisite complement of skills exists within it or is sufficiently accessible and responsive elsewhere. Indeed, one of the various arguments for having a core of engineering skills within bulk

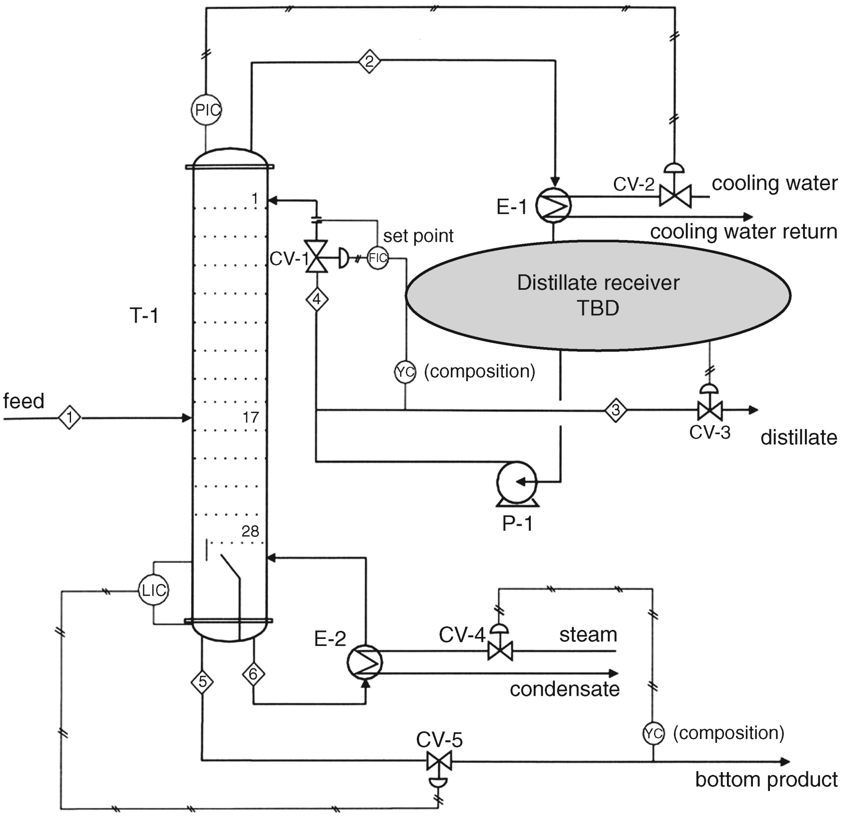

PIC
2
E-1
CV-2
cooling water
cooling water return
1
set point
CV-1
FIC
4
Distillate receiver
TBD
T-1
YC
(composition)
feed
1
17
3
CV-3
distillate
P-1
28
LIC
E-2
CV-4
steam
condensate
5
6
CV-5
YC
(composition)
bottom product

FIGURE 4 The "To be Determined" (TBD) provision in a P&ID. Although a very modest example is shown, the TBD provision is used as needed to indicate parts of the process design that may trail the overall design. This provision is particularly useful when the process design needs to move rapidly, sometimes at some risk that the outcome of the TBD item may require redoing some of the related design work. *Source*: Modified from Ref. 1.

drug chemical development is the ability to take snapshots of the developing process and do a good deal of informal and intimate process design or *back-of-an-envelope* design—e.g., is this the manufacturing plant we wish to operate? Or would this plant be amenable to ready expansion? Such snapshots permit swift sifting of approaches and choices, more rapidly adjust the bench and pilot efforts, and spare formal process design effort for more mature versions of the process. For projects with capital or product cost sensitivities, the snapshots also permit rapid estimation of the alternatives.

B. Process Design as the First Stage of Technology Transfer

Examination of Figures 1 and 2 confirms the previous assertion that process design is the first stage of technology transfer or, at the very least, provides the opportunity to initiate technology transfer to the advantage of the project. This is because in most drug manufacturers, the process design function (to whatever

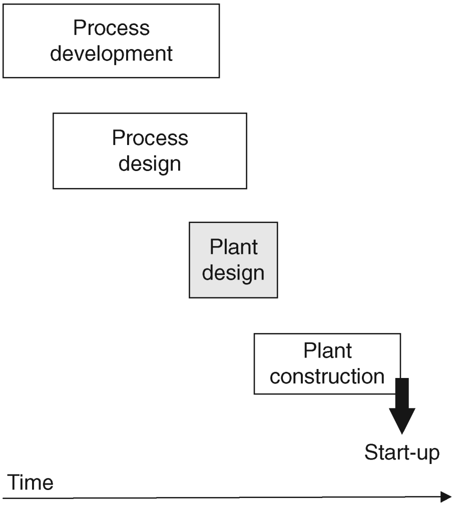


FIGURE 5 Plant design as the sequel to process design. The ability to compress the overall time cycle to first manufacture also depends on the extent to which process and plant design can overlap and permit earliest plant construction activity. The instance of retrofit into existing plant, although generally providing for the shortest cycle, can be adversely affected if the development and design overlaps miss an essential equipment item that is not at hand.

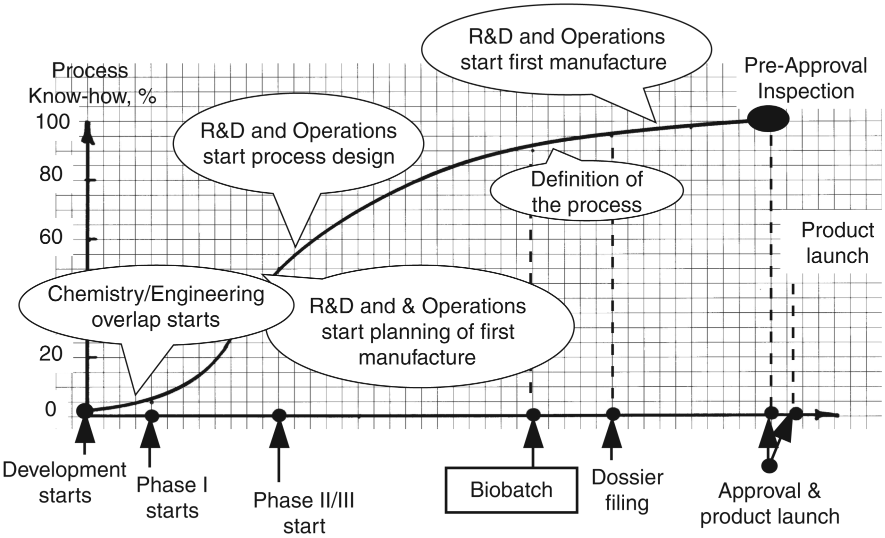


FIGURE 6 An eagle's eye view—from process development to plant start-up. The earliest start of planning and process design for manufacture as overlapping activities with process development provides the best chance of earliest first manufacture.

extent it applies to the project—new plant or retrofit) is associated with the first manufacture of the product, and the know-how of the developing process begins to reach the operational organization as process design begins. In both figures the increasingly heavier arrows, as the project progresses, indicate the know-how flow and the corresponding feedback across the development-design boundary. This fact is also apparent in Figure 6, where process design begins when the process know-how *begins to take its eventual shape.*

Participation in the development learning curve, reasonably close for the process design function and somewhat distant for the manufacturing function, can be very beneficial to the overall project, albeit at times the inevitable vicissitudes of process development cause distracting anxieties on the downstream side of the development team—an occasion for the appropriate managements to becalm the situation. Nevertheless, the opportunity for the operational side to prepare for the technology transfer and first manufacture is excellent, and an exemplary mechanism for such transfer will be presented in the section "Technology Transfer of the Bulk Drug Process and First Manufacture."

However, the current prevalence of outsourcing and the frequent use of engineering design firms have created an environment in which technology transfer takes place in a variety of ways and sometimes not at all, as we will discuss. Unfortunately, the tidy arrangement of doing everything in-house, as illustrated in the said figures, is gradually giving way to drug companies that manufacture only the very last stages of the chemical process. Nevertheless, the principles, also illustrated in those figures, are sound indeed, and good efforts to incorporate as much of them into whatever development-design or development-first manufacture boundary applies are worthwhile.

C. The Process Design Demands on the Process Body of Knowledge

The demands of overlapping process design with the development of the chemical process are more immediate and somewhat less rigorous than those of the dossier and of the final process design or the formal technology transfer events. Instead, good communications are essential (those back and forth arrows in Figs. 1 and 2 again), preferably complemented with brief written reports when necessary. Apart from clarity and accuracy, timeliness is the next most precious quality of the information exchange that undergirds the overlap of process development and design. In other words, the snapshots of the developing process need to be rapidly examined through process design as required by the scope of the changes being introduced or contemplated.

Beyond those demands, the process design function will eventually need the complete and fully organized body of knowledge (Table 4 of chap. 2) so as to permit

a. process design,
b. plant design (project engineering design and construction),
c. procurement of materials,
d. preparation of start-up plans and operating procedures,
e. assessment of the process safety issues in the specific context of the plant: operational safety, industrial hygiene, thermochemical, and environmental safety,
f. assembly (and timely approval) of environmental and other regulatory permits,
g. definition of the process start-up targets of yield, capacity, waste loads, etc., and
h. dealing with assorted other matters, such as those arising from the plant's insurance, etc.

Aside from the procurement of laboratory equipment through the capital project, the information needed for the transfer of the in-process and QC

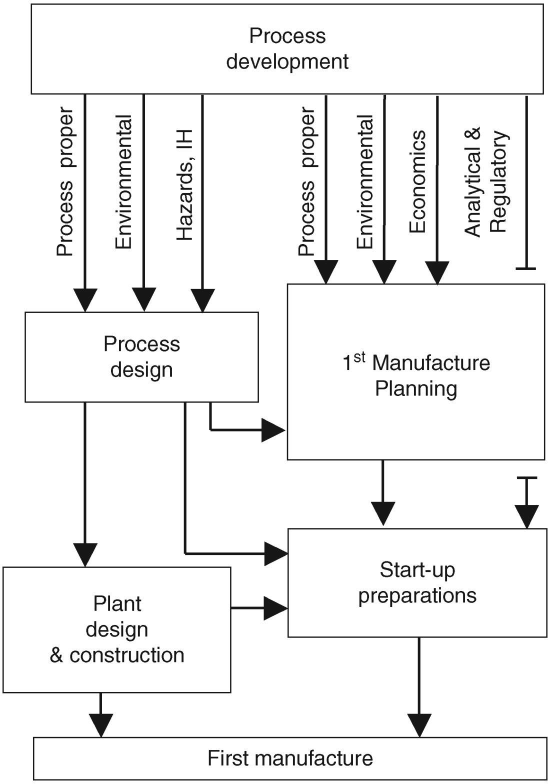

Process development
Process proper
Environmental
Hazards, IH
Process proper
Environmental
Economics
Analytical & Regulatory
Process design
1st Manufacture Planning
Start-up preparations
Plant design & construction
First manufacture

FIGURE 7 A model for the flow of the process body of knowledge. Successful first manufacture (timely, sufficient, and reliable) depends not only on the assembly of the requisite process body of knowledge, but also on its timely flow to the various downstream activities. The model shown above has worked well in each of numerous instances that the author has seen it applied.

analytical methods need not go through process design and may pass directly to the manufacturing organization (QA/QC included).

Figure 7 depicts a proven model for the flow of the process body of knowledge as it is applied to process design and first manufacture.

III. TECHNOLOGY TRANSFER OF THE BULK DRUG PROCESS AND FIRST MANUFACTURE

A. Definition and Scope of the Technology Transfer

Technology transfer has become the term that more appropriately describes all the events associated with the first manufacture of a new bulk drug (or for that matter, of any new product with its own distinct process for manufacture, which will usually come from without the manufacturing environment). Older and not-so-old practitioners are probably more comfortable with less comprehensive but very descriptive terms, such as "process start-up" or "process demonstration."

In its broadest definition, so as to capture all the activities for its execution, the scope of bulk drug technology transfer encompasses the tasks listed in the following text. (Here the reader is encouraged to place bookmarks on Figs. 10 and 12 for perusal, as well as review the approximate Gantt chart for the overall technology transfer in Fig. 8.)

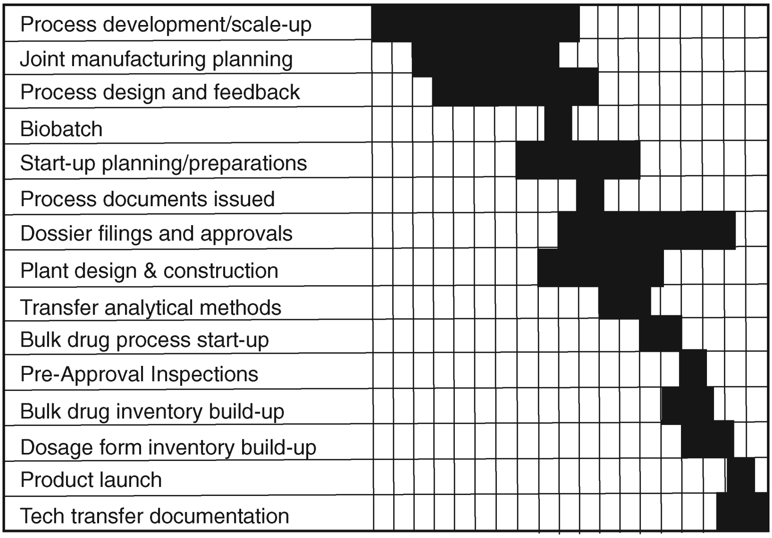


FIGURE 8 Gantt chart for the technology transfer of the chemical process for a new bulk drug: The chart shows all of the key components of the overall task, with an approximate indication of their relative positions on the time-to-market cycle and, to a less precise extent, of the relative widths of their timelines; the latter can vary considerably as a function of the process scope, new plant versus retrofit into existing plant and in-house versus extent of outsourcing.

Early stage (around the time that a new drug candidate enters development; i.e., it has shown enough potential to be worthy of the greater effort to follow, as indicated in Fig. 6, chapter 2):

a. The operations area acknowledges the task of a probable first manufacture tied to an expectation of regulatory approvals to market a new drug.
b. At the same time, the process development function acknowledges its share of the above-mentioned task—providing the technology for the safe, dependable, and timely execution of the first manufacture.
c. The need for probable capital approvals and subsequent expenditures is forecasted, presumably within the parameters of an established longer range plan that includes the launch of the new drug product as a probable event.

Next stage:

d. The process development function begins its collaboration with the operations area in addressing the broad-brush definitions of the project (as set out in list 1 under sect. "Definition and Scope of Process Design").

Next stage:

e. Overlapping process development, design and manufacturing planning takes place.
f. Capital approvals are sought, in portions and from a range forecasted for the total project.
g. Starting material sources are developed and business terms negotiated (this may include extensive outsourcing of, say, intermediates manufacture).

Next stage (some time after the biobatch milestone, but before filings from the dossier take place):

h. The process body of knowledge is documented.
i. The final process design is completed.
j. The plant design is completed and installation work proceeds.
k. Starting materials and auxiliaries are purchased.
l. Start-up plans and operating procedures are developed.
m. In-process, QC, and regulatory methods (stability) are transferred.
n. Process safety issues in the specific context of the plant are settled: operational safety, industrial hygiene, thermochemical and environmental safety.
o. Environmental and other regulatory permits are assembled and filed, and approvals obtained.
p. The process start-up targets of yield, product quality, capacity, waste loads, etc., are defined.
q. The process validation plan is defined.
r. The process start-up team is assembled.
s. The plant installation is tested and readied for the process.
t. The process is started up and validated.
u. Pre-approval inspections (PAI) take place.
v. Process consolidation—the start-up continues to demonstrate all targets under p.
w. Results are documented, including updated operating procedures, in-process controls, etc. Heads of the start-up team sign off.
x. Mechanical/instrumentation items, Punch list and the To-Do list are prepared.
y. The start-up team is disbanded, but liaison persons are designated for matters arising. Manufacturing takes over.

The reader should beware that hidden within the above reassuring list are all the necessary actions to solve unexpected problems, particularly those arising during process start-up, validation, and consolidation, or those in response to significant observations from PAI. Difficulties in technology transfer are inevitable; no such large number of activities that must dovetail precisely can go without some adversity or something being overlooked. Yet, *well-executed* projects for complex chemical processes generally meet their targets of bulk drug deliveries, and the existing process body of knowledge and assembled resources permit swift resolution of arising difficulties.

An approximate sequence of events *following* the designated validation work (and its follow-up) that is useful for planning purposes is as follows (assumes a multistep process of significant scope):

During validation—25% of design capacity is reached.
Month 2—60% of design capacity is reached.
Month 3—80% of design capacity is reached. All lots are without quality issues.
Month 4—100% of design capacity is reached. All lots are without quality issues.
Month 5—Procedures updated. Summary memorandum on results is signed off and issued.
Month 6—Operating personnel training confirmed (but meant to continue). Comprehensive process start-up document issued.

Obviously, the above timetable will vary with the scope of the process start-up: number of steps, number of plant sites, intrinsic process complexity, time cycle (e.g., long fermentation cycles plus downstream processing plus any semi-synthesis to follow). Sensible allowances to the above figures should be made.

B. Mechanisms for Technology Transfer

There are as many technology transfer mechanisms as there are operational arrangements in bulk drug manufacturing. However, the practice of technology transfer within research-based drug companies can be said to take place within either of two environments:

1. R&D driven. In this arrangement, the R&D division delivers, through its process development organization, a complete process to the operations division, which generally uses its process design function as the *principal* gate to receive the process. While some specifics may vary from instance to instance, the technology transfer (as just defined under sect. "Definition and Scope of Process Design") takes place along the following lines:

   > R&D bears the principal responsibility for the technical success—it *demonstrates* its process to the operations division. Accordingly, R&D leads the effort and casts a heavier vote on decisions bearing on the process and its operation, not unlike a first among equals. R&D also acts as the technical liaison with contract manufacturers and transfers its process or chemistry to them, and eventually sponsors the suitability of materials from those contract manufacturers.

   This environment offers the decisive advantage of *a single handover*—from the development activity in R&D to a performing plant that delivers bulk drug as required, and with reasonably well-defined responsibilities. Indeed, technology transfer is an activity with all the vulnerabilities of a handover, and the analogy with certain sports is quite apt, thus the advantage of a single transfer. Figure 9 attempts to describe the R&D-driven environment for technology transfer.
2. Stage-wise. In this arrangement, the process development is split along disciplines or along operational lines, causing more than one handover and with a greater spread of the technical responsibilities (Figure 10):
   a. The synthesis (or biosynthesis) and its analytical components are delivered by the R&D division (chemists and microbiologists only) to an arm of the operating division that has the engineering and pilot plant resources. Obviously, the delivery of the chemistry must be in stages as it develops, as the bulk drug supply to drug development is the responsibility of the operations group. Eventually, the latter transfers the process to manufacturing.
   b. The R&D division delivers the process to the operations area at some intermediate stage of development at which the chemistry has been established, with the rest of the development completed in the operations area. The developmental bulk drug supply is a shared responsibility, allocated according to ownership or control of pilot scale resources.

Regardless of the mechanism, however, all the activities under section "Definition and Scope of Process Design" need to be carried out, even if less

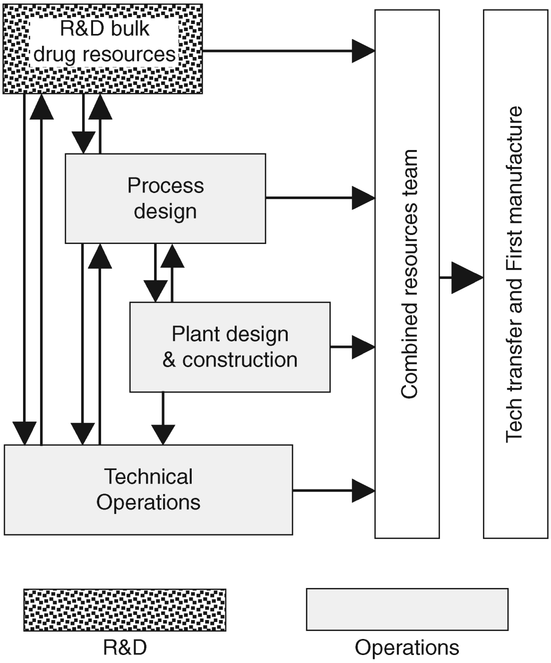

R&D bulk drug resources
Process design
Plant design & construction
Technical Operations
Combined resources team
Tech transfer and First manufacture
R&D
Operations

FIGURE 9 Technology transfer mechanisms—R&D driven. All of the process know-how flows from R&D organization to operations (manufacturing), outsources, or both, although the diagram depicts the in-house case.

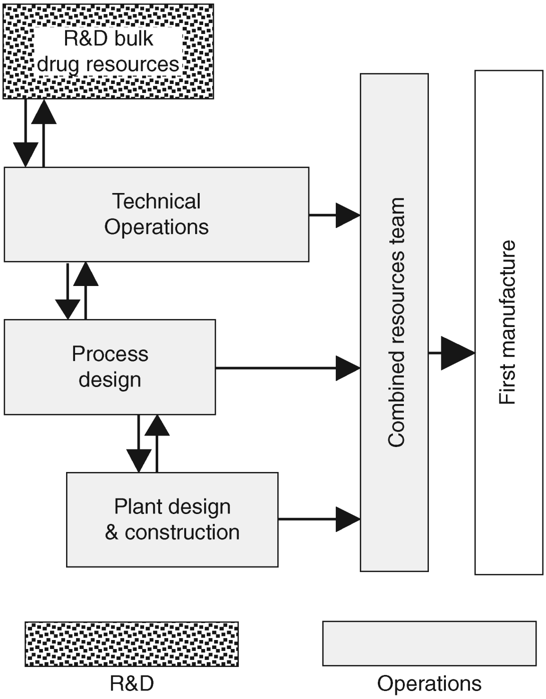

R&D bulk drug resources
Technical Operations
Process design
Plant design & construction
Combined resources team
First manufacture
R&D
Operations

FIGURE 10 Technology transfer mechanisms—Stage-wise across operational boundaries. Either a partially developed process or a developed process (through the last intermediate material) is transferred to the technical arm of the operations area, which carries out the first manufacture activity, with R&D playing a secondary or contingent role during the latter. Most often this mechanism results in two technology transfers.

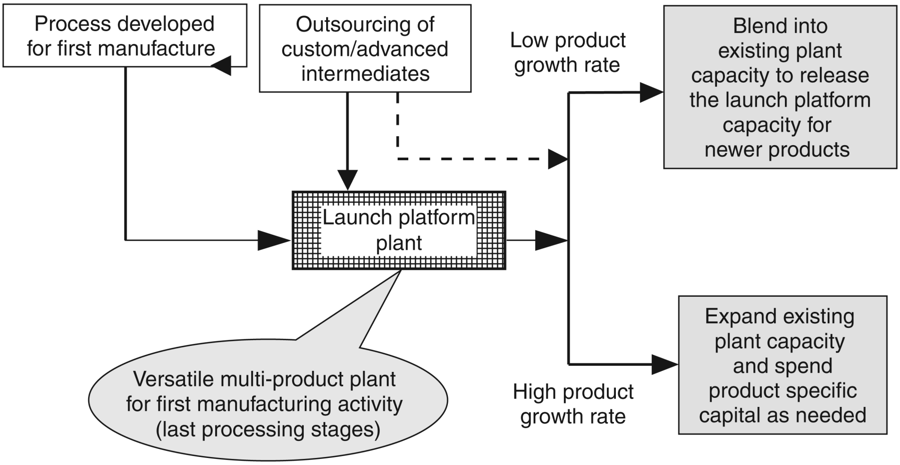
tidily. The same is true for those frequent cases in which the sequence of process steps is divided among more than one manufacturing site. Even less tidily, the same is true for projects with significant outsourcing, certainly to the extent that the processes are reliably established at each supplier.

In recent years, the advent of the USFDA PAI method (and analogous inspections from agencies outside of the United States) has spawned the "launch platform plant"—a multiproduct chemical plant designed for versatility, faster turnaround between products and capable of manufacturing a new bulk drug (or more than one new bulk drug) until the full range of regulatory approvals and sales growth justify the transfer to another plant of larger capacity as a longer term home for manufacture. This plant concept is discussed further in Figure 11.

As to the technology transfer resources that must come together at the appropriate time, they range wide across both R&D and operations:

From R&D—Process chemistry and process microbiology
Chemical engineering
Analytical R&D
CMC team that prepared the process input to the dossier
From operations—Process design
Plant design and installation (and their contractors)
Technical services (divisional or from the site of manufacturing)
Production (from the manufacturing site)
Plant engineering
QA/QC
Operational, health, and environmental safety
Materials management (divisional and site of manufacturing)

While some of the above players carry out crucial support roles and are active in the day-to-day effort of starting up a new process, the principal burden



Process developed for first manufacture
Outsourcing of custom/advanced intermediates
Low product growth rate
Blend into existing plant capacity to release the launch platform capacity for newer products
Launch platform plant
Versatile multi-product plant for first manufacturing activity (last processing stages)
High product growth rate
Expand existing plant capacity and spend product specific capital as needed

FIGURE 11 The Launch Platform Plant. A device aimed at avoiding a significant plant construction task by retrofit of the new bulk drug process into an existing plant dedicated to first manufacture only.

rests with those with their hands on the actual operation, the process designers, and the immediate laboratory support (testing, ad hoc experiments to obtain a missing datum, validate a hypothesis on a problem, or run a process manipulation in parallel to the plant). They have not only the task of demonstrating the process in new or modified equipment but also that of training the operating personnel.

Some commonsense and well-proven prescriptions are as follows:

- A detailed log of events, preferably in clear English prose and with comprehensive entries, is essential. The "Manufacturing Operating Instructions" or whatever formal record of the processing is created will generally be far too structured as a series of instructions and blanks for data and signatures, ditto for logs from the control computer system, if any.
- As suggested above, the plant technical services laboratories should be dedicated to support the process start-up around the clock in speedy and unstructured ways that QC cannot.
- The process start-up team should be well staffed in numbers and in the representation of all the skills and experience accumulated during the development and process design, set to apply more-than-sufficient power to the task, and *make rescue missions unnecessary.*
- All background documentation, from the development, the process design, and the installation, should be at hand and well organized for swift location of needed information.
- Operations management should keep its oversight discreet and be disciplined with respect to distracting the start-up team for the latest, particularly at times of stress.
- There should be at least one review meeting a day, attended by the principals of development, process design, analytical services, technical services, production, and project engineering (installation), run sharply and to the point, with "who does what by when" unambiguously defined.
- Data and other trends should be followed, preferably from some premeditated plan, so that the direction of process performance can be assessed soonest.

Finally, a technology transfer device that works very well in avoiding pitched battles upon process start-up problems—where are the funds to fix the problems?—is to have a fixed amount of the capital budget for the project allocated as a contingency to such fixes and *under the control of the start-up team.* This protects the process start-up from a shortfall of funds due to underestimation of the original installed cost of the plant. A total of 5% of the total capital budget is usually a sound allocation for such contingency. The latter is, of course, apart from the usual 15% contingency of such capital projects, and is given back to the corporation if not used (by keeping it out of the grasp of the plant manager).

C. Technology Transfer in the Outsourcing and Licensing Environment

Up to this point, we have alluded to the outsourcing environment while describing systems and prescribing ways of operating largely in the context of a big pharma organization, where all the capabilities exist under, ultimately, a single management. This has been useful in that it has permitted presenting the tasks of process development and technology transfer comprehensively. Indeed, the tasks at hand are basically the same and need to be performed just as well without regard to how the tasks might be divided between the various parties in the current outsourcing environment for bulk drug manufacture. As of this writing in mid-2009, however, it is clear that pharma has significantly deepened its commitment to the outsourcing of bulk drug manufacturing, well beyond that of advanced intermediates and with a greater impact on the technology transfer task across the outsourcing boundary.

Therefore, we need to understand the complexities added to the basic tasks by their becoming divided among

- customers, ranging from big pharma to virtual and "almost virtual" drug companies,
- suppliers, ranging from large fine chemicals manufacturers to small new companies with a claim to some niche processing technology, and
- service providers, offering to take only the customer's compound structure and perform it all through first manufacture (generally relatively new and small companies), thus appealing most directly to the virtual and almost virtual customers.

> Virtual drug companies are those that generally possess nothing more than the patents or the licenses to a compound, and operate by contracting all subsequent tasks. Almost virtual companies are those that, although having discovery and some clinical development capabilities, lack everything else.

Starting with the big pharma customer, the technology transfer task takes place in a relatively narrow range defined by the following poles:

- The customer wishes to outsource part or all of the bulk drug manufacturing, using one or more contract manufacturers. The customer also brings sufficient process know-how and assumes the responsibility of demonstrating its performance in the manufacturer's plant, according to a *well-defined process start-up plan* jointly developed by the two parties (2). Figure 12 describes this happy set of circumstances, clearly the best

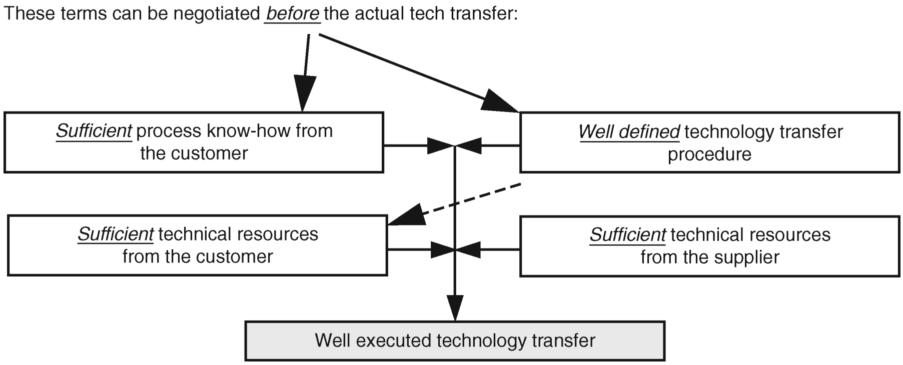

These terms can be negotiated *before* the actual tech transfer:
Sufficient process know-how from the customer
Well defined technology transfer procedure
Sufficient technical resources from the customer
Sufficient technical resources from the supplier
Well executed technology transfer

FIGURE 12 Technology transfer in the outsourcing environment—The optimal scenario, shown on the basis of the well-managed transfer of sufficient process know to a capable recipient.

scenario for technology transfer between the customer (who has the technology) and the contractor (who has the plant and the right set of manufacturing conditions).

- The customer and the contractor come together on the presumption that the contractor's processing skills, plant capacity, and existing chemistry operations (with its available intermediates) constitute a significant advantage (time and cost) as a supplier of a given compound, generally an advanced intermediate. The customer may contribute all or part of the process for the conversion of the contractor's intermediate to the former's target, although often enough the latter contributes to the actual process.

> Both poles define a range in which technology transfer is greatly facilitated by the existence of a sufficiently developed process from the customer (in the first case, Fig. 12) or, in the second case, by the relative ease in reaching the target structure from the contractor's existing intermediate, with or without some process development collaboration.

However, on the other end of the spectrum, the virtual and almost virtual customers have no process technology of their own and thus seek one or more contractors that will make the compound on the basis of their existing offerings of proximate intermediates. Here the customer has no technology to transfer, and the matter resides entirely with the contractors. There is, however, a scenario that is increasingly found in the virtual and almost virtual customer domain and that can be best described as the "technology transfer from hell," which a mere examination of Figure 13 will confirm.

> Most cases of a compound being licensed to a virtual or almost virtual company bring no process technology (beyond medicinal chemistry and preliminary preparations) or partially developed processes. Thus, the licensor is, at best, in a weak position to transfer useful or complete process technology and usually lacks

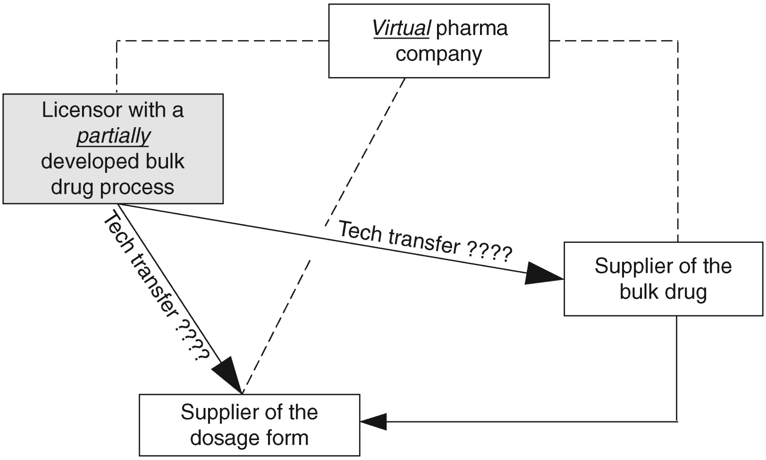

Virtual pharma company
Licensor with a *partially* developed bulk drug process
Tech transfer ????
Tech transfer ????
Supplier of the bulk drug
Supplier of the dosage form

FIGURE 13 Technology transfer in the outsourcing environment—The worst scenario, shown on the basis of a virtual company that licenses a compound that does not bring a sufficient process body of knowledge.

motivation beyond the precise letter of the license. Also in most such cases, the virtual or almost virtual customer lacks processing background or experience in the fine chemicals milieu, or hires people with such competency much too late.

While some of the above difficulties are inherent to the virtual character of the customer, the latter can take some actions to avoid the "technology transfer from hell," namely:

- Hire or engage competent people in chemical manufacture, preferably with experience in dealing with fine chemicals manufacturers, and preferably right at the outset of mounting a serious clinical effort (3).
- Seek license language that unambiguously obligates the licensor to provide full documentation of the process and its experience with it (in a manner suitable for input to a dossier), as well as an ironclad obligation to a serious technology transfer effort. Use milestone payments as a means to motivate the licensor on the latter.

The licensee should beware of accepting the licensor's "production documents" as the core of the process documentation, as such documents—operating procedures with the blanks filled in—are poor vehicles for imparting process knowledge. To the extent that it exists, the process body of knowledge should be well documented and provided by the licensor, along the lines described in the section "The Process Body of Knowledge" of chapter 2.

- Obtain an independent evaluation (not from the licensor or the potential contract manufacturers) of the development status of the bulk drug process relative to its first manufacture *and* of the readiness of the resulting bulk drug for successful manufacture of the desired dosage forms. If development is not complete, seek its completion in a competent environment rather than patching it up at the contract manufacturer or by hiring a modicum of staff to rush it through in hastily arranged laboratories.
- Manage its QA and regulatory team as *earnest participants* in establishing the bulk drug activity rather than approaching it strictly as a *policing task*.

D. Regulatory Aspects of Technology Transfer

The principal regulatory task in the technology transfer of a bulk drug process is its reduction to practice in accord with the process defined in the dossier and to develop and execute a sufficient (not an excessive) validation plan. It is also important to do so at a contractor or contractors that understand the basis and procedures of the drug master file system and their obligations to the customer's dossier; having a good manufacturing practice (GMP) status is not sufficient, as the latter is the minimum requirement. The customer should scrutinize those aspects of the contractor's operations early in the due diligence process, including its change control procedures.

Preparedness for PAI is not a trivial matter, as significant observations may delay the approval of the corresponding applications; usually the PAI takes place after all other aspects of the application have been reviewed and found suitable for approval. Although GMP issues may arise, the principal objective of the PAI is to determine the soundness of the manufacturing process relative to the process described in the application. Some golden rules that can do no harm are as follows:

- Be prepared to credibly answer questions on the spot (all knowledgeable personnel immediately available, all documents organized and handy). Questions should not linger unanswered because of not being prepared.
- Assume the inspector wants to know if you know what you are doing and that the scientific and technical background of the process has been mastered by those who will run it.

E. Transition to Mature Manufacture

Successful transition to mature manufacture (different from static or declining manufacture!) requires, of course, the firm basis of a sound and well-documented technology transfer, including a list of all the To-Do items (those actions of modest scope that would consolidate and improve the reliability of the process and its operation). The process training of the operating personnel also needs to be consolidated, avoiding the feeling of security suggested by their familiarity with the production documents and the manipulations fresh off the process start-up. In other words, *consolidation of the new manufacturing operation* is the foremost objective after technology transfer.

Next, the To-Do list should be executed promptly within the change control procedure. Measures for increasing production output should be conceived and taken as far as planning in the event of product growth. If the latter is already anticipated with some precision, those measures should be pursued deliberately.

If expedients with respect to raw materials were used to get to first manufacture (e.g., a single supplier of a critical material and a risky inventory position on another), those need to be addressed immediately, particularly if expanded output is desired. On the other hand, superfluous requests to qualify new suppliers (usually coming from materials management) should be rejected for the time being.

Process changes for cost reduction should be pursued first on the basis of their technical soundness and merit, and then on the basis of their cost impact, but mindful of the possible introduction of too many changes too soon, as well as of the vicissitudes of supplemental submissions to the regulatory agencies. On the other hand, process changes aimed at increasing output, while scrutinized just as much, could be put on a track faster than those for cost reduction if firm production targets for the plant justify it.

In evaluating the above process changes, the original process body of knowledge should be mined with intensity, as invariably some good ideas and partially developed improvements have to be set aside during the original development if the dossier target dates are to be met.

For intermediates or bulk drugs made by contractors, the same approach embodied by the above recommendations should be sought in their operations, with particular attention to their observance of sound change control procedures and drug master file maintenance.

Figure 14 attempts to depict the sequence toward mature manufacture just outlined in order of priority.

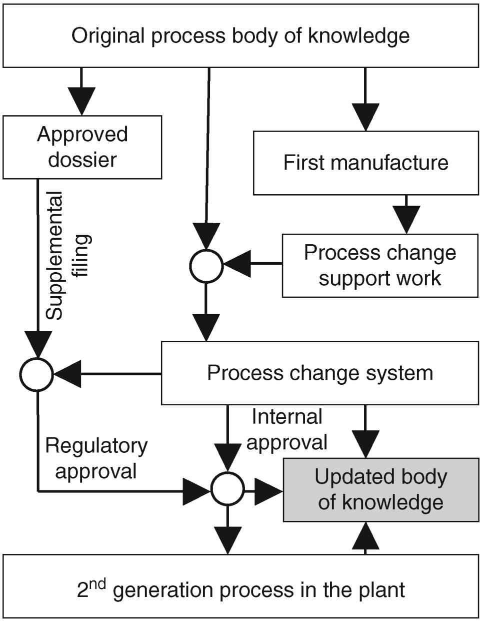

Original process body of knowledge
Approved dossier
First manufacture
Supplemental filing
Process change support work
Process change system
Internal approval
Regulatory approval
Updated body of knowledge
2nd generation process in the plant

FIGURE 14 From first manufacture to mature manufacture. The process change mechanism that leads, over time and various process and operational changes, to a mature manufacturing operation that supports product growth and reduces the cost of goods.

IV. IN CLOSING—THE PROCESSING TECHNOLOGIES OF BULK DRUGS

It is not in the scope of this chapter to address this topic in any breadth and least of all in any depth. The variety of the technologies is too large and the field far too rich. Instead, some selected observations that the new practitioner might find useful follow.

1. Process development organizations that lack a sufficient engineering component often miss the opportunity of the better implementation of the chemistry by shunning continuous processing. It is not a matter of disdain, but of not having the tools, and often enough, the pull of the familiar batch or semi-batch methods is too powerful.
2. Product purity and consistency, which are paramount norms in bulk drug manufacturing, are today observed through the impurity profiles to an unprecedented extent. This puts a great deal of pressure on the mastery of purification methods, mostly on those based on crystallization from solution.
3. A final recrystallization of the bulk drug for the purpose of a consistent composition of matter from which the material emerges has considerable advantages in providing consistency of the physicochemical attributes of the bulk drug, including the control of phase purity (single and consistent polymorph). It also buffers the bulk drug from vagaries upstream and tends to becalm regulatory disquiet, particularly about process changes upstream.
4. Scale-up of chemical processes is a business of much skill, largely because the frequent intrusion of physical effects on the chemical kinetics. Good predictive tools and solutions exist, however, to deal with those intrusions

by changing the physical environment away from that of the bench scale experience, but requiring the application of chemical engineering skills and the willingness to abandon the familiar batch or semi-batch stirred tank when necessary or advantageous.

5. The bulk drug-dosage form boundary of process development is very difficult, often because of the discipline differences and just as often because the definitive decisions on the dosage form side come late in the cycle (often for good and largely unavoidable reasons). The bulk team must be sensitive and skilled in delivering to the dosage team what they need, and get very involved with their issues early in the development cycle, particularly to seek multidisciplinary decisions.
6. Practically all prescriptions for sound and successful bulk drug manufacture given in this chapter apply to the varied, seemingly tumultuous outsourcing environment, but only if a diligent effort goes into operating, maintaining, and building trust in the customer-supplier relationships.

In closing, few industrial endeavors offer as many opportunities for exciting and valuable technical work as the development of processes for bulk drugs and their implementation in performing chemical plants. The merging of chemistry (in its various fields), microbiology, chemical engineering, and pharmaceutics makes it possible, but demands that the practitioner of a discipline be earnest in the interaction with the others, regardless of their disciplines or their functions. Only through such effective interactions can success be reached in the exciting and difficult business of bulk drugs.

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4 Design and Construction of API Manufacturing Facilities

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I. INTRODUCTION

The design and construction of API (active pharmaceutical ingredient) manufacturing facilities is one of the more challenging assignments in the engineering and construction business. The successful completion of a new API process facility is a function of accurate process definition, a robust project execution strategy, good engineering practices, sound construction techniques, and a well-planned and documented start-up and validation plan. Early detailed process definition enables the project team to develop a comprehensive project execution strategy. The execution strategy outlines the engineering and construction methods for the project. The start-up and validation plan ensures regulatory compliance and a smooth transition from construction to operation. API production facilities are technically complex and expensive to design, construct, and validate. New facilities require sophisticated processing equipment, utilities, and support functions. Careful planning and good sound engineering are critical to assure that the investment in capital is managed wisely.

The reader must be familiar with the requirements of current good manufacturing practices (cGMPs) for APIs. The engineer/engineering firm/designer will be responsible for the design of facilities and systems that will meet cGMPs for API manufacturing. The constructor will be required to install and validate the equipment and facilities to meet the same criteria. Certain systems, such as process water and HVAC (heating, ventilating, and air-conditioning), are required to meet specific regulated criteria. Details of validation and cGMPs are discussed in other sections of the manual. We will focus on the impact on design and construction by validation and cGMP considerations.

Various strategies utilized in the engineering and construction of new production capabilities, whether they are new facilities or renovations to existing capacities, are presented. A clear execution strategy and the need to understand the scope of the project are important components that are reviewed in detail. Management of the design process is critical to success. The firm must be able to properly manage the development of the design, ensuring that the process is complete and "frozen" prior to the commencement of construction.

A clear decision-making process will minimize the churn and delays. Developing a design and construction scope requires many decisions to be made in a timely organized fashion. These decisions have major impacts on the operability, safety, and compliance of the new facility. The team charged with the responsibility for the new API facility must utilize a strong decision-making process. Techniques such as lean process and six sigma analysis will strongly aid the process.

An API project is created when a need arises through one or more of several reasons. Some examples include (1) new product introduction, (2) regulatory change requirements, (3) existing product capacity shortfalls, and (4) process improvements. Any one, or combination of these areas, can generate the need for a new capital investment.

The engineering and construction steps are similar for the four stated cases. Excellent scope definition and a well-thought-out execution strategy are required for all of them. A firm will analyze many different manufacturing options before establishing the final project scope. The most uncertainty occurs with the new product introduction. The firm can be required to develop a preliminary scope of work during early stages of process development. There is a higher probability of design change and process churn as the new process develops. The firm must be prepared to manage facility and equipment changes as the new process is finalized. The key to success is minimizing/mitigating the changes.

The other business cases normally have a defined process within existing operating facilities and with known market volumes, having already been on the market. The major process components have already been defined and possibly are operational. The process is a regulatory agency-approved process which has proven viability. Normally, the changes associated with these types of projects are limited in scope to process enhancements, that is, increasing throughput, eliminating bottlenecks, increasing yields, etc. This chapter will not focus the discussion on these types of projects.

This chapter focuses on the requirements of engineering and construction of facilities for a new API. This can be the most challenging task because the technology very possibly is untested on a commercial scale by the manufacturer. Inherently, there are technical assumptions that carry associated risks. Assuming the product and the process are untried at commercial scale, there can be unforeseen issues with start-up and operation that arise at the proposed scale for the new API entity. Certain components of the process, such as product handling and transfer, and material consistency, may become an issue at the production scale that was not detected in a pilot or bench operation. The design team must take into consideration any components of the process that will not be a scaled-up duplication of the laboratory version of the process.

The risk of a pump or product transfer system not working properly because of material viscosity or incompatibility may require changes to the process once the system is built. Material handling aspects through equipment such as centrifuges, blenders, or mills can be different from the smaller scale experience. Common problems that develop at commercial scales include pumps not operating as designed, material bridging in centrifuges, and blenders/dryers, and different milling consistencies. The engineering and construction team may be required to change components during the initial production runs of a new compound. A good designer will incorporate the necessary flexibility in the new process to allow for equipment changeouts. The design of equipment should incorporate the ability to replace it or upgrade in a manageable fashion. The commissioning stage of a project will identify most material transfer and process issues.

A benefit for the readers is the ability to utilize this strategy for other process improvement or regulatory-driven projects. The steps are similar, if not the same (the major differences are associated with the business and engineering analyses for the new API).

Many of the terms and references in this section are typical of fine chemical manufacturing. We will assume the reader has an understanding of this process.

II. PROJECT SCOPE DEVELOPMENT

A. Capacity

Market projections will indicate required volumes of the new API. Unfortunately, market projections can vary widely. Manufacturing capacity for a new API facility is expensive to build, maintain, and operate. It is important to "properly size" the production processing equipment and supporting facilities. A recommended engineering approach will be to incorporate the ability to expand a production facility or equipment train(s) allowing for future expansion if volumes do increase. The future expansion planning can be as simple as incorporating the footings for a building expansion during construction of a new facility, or can be as complex as adding an additional bay to a new or existing building along with all associated utilities for that future expansion.

A key component of the analysis is whether to produce the new API with dedicated process trains and facilities or to campaign the new product with other products utilizing similar equipment. Major new API compounds may warrant dedicated process trains and facilities due to the sheer volume of product or due to unique processing techniques. However, most new higher potency APIs can be produced with less equipment over a shorter time span than in the past, thus allowing the manufacturer to produce multiple products within the same equipment. This approach can often result in significant conservation of capital.

B. Siting

The new facility can be located in any of the major markets in the world. Business reasons can be very diverse—locating near existing operations, low-cost tax jurisdictions, new emerging markets, etc. The decision to locate a facility must balance the business needs with the other factors, including construction markets, regional environmental capabilities, and robust regional infrastructure.

Labor markets are an important component of the analysis. The technical skills required to operate and maintain the facility, and for construction and start-up, are sophisticated. Complex processes require skilled technicians to run the process. Skilled mechanics will be required to maintain the facility.

Sophisticated equipment and facilities require skilled labor and construction professionals. It is difficult to construct and maintain one of these facilities in a remote part of the world and in certain parts of the United States. Labor markets are limited. The new facility may compete with other facilities under construction for the available labor and construction support resources. Major API and biotechnology projects have recently experienced large cost impacts, both in the United States and foreign locations, because of a dearth of trained construction and engineering professionals for these facilities. Site selection should be one that offers an acceptable supply of operational support and construction resources. Execution strategies for the construction of the facility(s) will be impacted by the ability to attract skilled labor and materials. We discuss prefabrication/modularization as a viable option for these and other conditions.

Other conditions to consider are off-site capabilities for waste treatment and disposable, hazardous waste disposal, along with reliable power sources.

C. Project Execution Strategies

Once the API manufacturers have generated enough preliminary information for the new process, they will have several options for implementation of the design and construction of the new facility. There are various execution strategies, which include:

1. Design and construction utilizing an engineering firm(s) and a construction contractor(s)
2. Design and construction utilizing an engineering firm(s) and a construction management firm(s)
3. Utilizing one firm to provide engineering, procurement and construction management (EPCM) services
4. Design and prefabrication of processing modules with a construction contractor

The EPCM strategy is well suited for a manufacturing firm that does not have depth within its own engineering and procurement organizations. This method places all the responsibility on the engineering contractor to deliver a finished GMP-compliant facility. The firm selected must have the personnel depth to be able to supply all facets of the project. This method tends to be the most effective for schedule, but can carry cost premiums. The EPCM contractor assumes all the risks on the project and will charge a premium for assuming the risk.

Methods 1 and 2 will work well with manufacturing firms that have established plant and construction engineering groups. The first method, design and contract, is the "traditional" method of construction. The design is completed and the project bid. The successful bidder has a lump-sum contract to complete the work. This method tends to take longer. However, in a competitive market, it can be the most cost-effective. The second method, utilizing a construction manager and separate design firm will enhance the schedule of the project by bidding work as it is designed and will control costs if properly executed. This chapter discusses these methods in detail later.

Method 4, utilizing prefabricated modules, is a recent option for the industry. Prefabricating modules reduce risks associated with field-constructing processing trains. The modules are prefabricated in an industrial manufacturing facility, precommissioned/tested and shipped to the site for installation. This method, which has been debated to be more expensive initially, will reduce risks associated with field variability (weather, skilled labor, etc.) and shortens the critical schedule durations for commissioning and start-ups. A schedule-driven project will benefit through modularization.

III. PRELIMINARY SCOPE DEVELOPMENT

The preliminary scope should include enough information for the engineer and constructors to start developing cost and schedule data. The information should include process flow diagrams (PFDs), piping and instrumentation diagrams (P&IDs), initial facility requirements, validation strategy, and a preliminary project execution strategy.

A preliminary scope of the new process should be developed in parallel with process chemistry, engineering development, and early piloting for the new API. The scope should also include a definition of the process, equipment specifications and requirements (vessel types and sizes), preliminary facility fit, permitting requirements (local building and environmental), and regulatory (cGMP) requirements. The producer's process engineering group or process consultant will have to determine the best process fit to ensure speed to market, cost-effective manufacturing, compliance with safety and environmental requirements, and GMP compliance.

A. Campaign Versus Dedicated

Many of the newer compounds developed for market are of a higher potency, reducing the need for large volumes of the API. A dedicated process may be the easiest approach to design and construct but may not be the most cost-effective or strategic. A dedicated process is ideal for a one product organization or high volume product. It may be easier to manage with unchanging processing parameters. Varying market product demand can impact usage of the facility and the cost of operations.

A campaign style facility will allow the manufacturer to better utilize assets, integrating different product manufacturing using similar equipment configurations. The producer has different options available for product volumes and production time. The campaigning facility will have different processing capabilities through various manifolds or hard piped equipment configurations (equipment trains). These configurations can be manipulated for different processes. This provides the manufacturer with the flexibility to vary production sequencing to produce several products versus one.

GMP requirements must be reviewed carefully with a campaigning style facility. Processing and building systems must assure no potential for contamination of API materials. GMP controls are applied with the use of API starting materials. The controls increase as process proceeds to final isolation and purification. The producer will be required to ensure GMP integrity for the new or renovated facility. Some of the considerations include proper product isolation (barrier separation), cleaning systems for multiproduct equipment (CIP, clean-in-place) and pharmaceutical grade water systems (for isolation and purification).

B. New Versus Retrofit

The API manufacturer will be required to decide whether a new facility will be required or an existing facility can be retrofitted. Questions that the manufacturer should ask include the following:

- What existing assets are available in the manufacturer's portfolio?
- Can these assets be modified to process the new product?
- What are the costs associated with the renovations? How do they compare to a new facility(s)?
- What renovations are required to qualify the process or facility?

It may appear financially more attractive to renovate an existing facility. The "bricks and mortar" costs are minimal. Infrastructure/utilities exist and may only require minor "tweaking." However, renovations and additions must account for GMP requirements. These requirements can substantially impact schedule and cost to a project.

IV. GMP CONSIDERATIONS

A careful cGMP review will be necessary as part of analyzing an existing facility for a new product fit. The current GMP guide for API facilities is the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use guide Q7A—referred to as ICH Q7A (1). Sections 4 and 5 cover all aspects of facility and process equipment requirements.

Section 4.10 of ICH Q7A states the following: "Buildings and facilities used in the manufacturer of intermediates and API's should be located, designed and constructed to facilitate cleaning, maintenance and operations as appropriate to the type and stage of manufacture." This section further outlines other considerations such as material flow, sanitary space for personnel, and separation of functions (lab vs. manufacturing).

Facilities currently manufacturing fine chemicals may not meet the standards outlined in ICH Q7A and not hold up under the scrutiny of a regulatory inspection. Major renovations may be required to retrofit an existing facility(s) to ensure GMP compliance. The manufacturer can be required to install new systems such as CIP and pharmaceutical grade process water. In product isolation/purification and finishing facilities, the manufacturer will have to ensure product separation in multiproduct suites through physical barriers, such as walls, and also through differential room pressurization with minimum room air exchanges.

Caveat Emptor—Understanding the requirements of a GMP facility is critical to developing an accurate cost and schedule model for the new product. A process fit that appears simple for a fine chemical could require substantial renovations for an API.

V. SAFETY AND ENVIRONMENTAL CONSIDERATIONS

Safety and environmental scope considerations are no different than that of the fine chemical industry. The facility will be handling hazardous materials: cytotoxic, flammable, corrosive, etc. The scope and design of the facility will include the necessary requirement to safely manage the hazards. Chapter 11, "Design and Operating Practices for Safety," discusses all aspects of hazardous facilities design.

Waste management will vary with siting locations. Early in the scope development process, the engineer will determine the best methods for managing waste streams. The scope and design of the facility will account for minimization and proper management of liquid, solid, and gaseous waste streams.

VI. DESIGN STRATEGY AND DETAILED DESIGN

The API manufacturers have essentially two choices in setting a design execution strategy. They may elect to develop the detailed design in-house with their own expertise, or they will obtain the services of an engineering firm/contractor who will provide the services for them. We will discuss the option of utilizing outside services for this function. The vast majority of manufacturing firms do not possess the "in-house" capabilities to develop the full breath of design for a new process facility or a major renovation.

There are various methods of employing the outside firm utilizing various contracting strategies. The firms can be hired on a reimbursable basis. This method is the most common in the industry. The firm is remunerated for all design services cost plus a markup for overhead and profit. Typically, the manufacturer will negotiate a contract with the design services supplier for a "not-to-exceed" value for the work. The design firm normally develops this estimate. It is impacted by the stage of process development. The more defined the process and scope of work, the better the estimate.

The other less common method is buying the design on a lump-sum basis. The design firm provides a firm price for the work. A careful definition of expectations is required for this approach. This contracting strategy is akin to using a building contractor for a home or commercial building. The pricing is based on a fixed set of parameters, which are normally the plans and specifications developed for projects. Any items not included in the plans and specifications are considered out of scope. All items out of scope of the contract are subject to extra charges. The lump-sum design contracting strategy is a difficult strategy for designing a new process with uncertainty. As design progresses, any changes to the process will result in negotiating change orders to the contract with the design firm. This method can create distractions to the design effort as the manufacturer and the engineer become involved in pricing negotiations. This method is more common with small process configuration changes in existing facilities.

Selecting the right firm and establishing clear expectations is critical to the success of the project. How the firm is utilized is a decision to be made in the planning stages of the project. The API manufacturer can elect to use the various methods of contracting for services that have been outlined in this chapter.

The execution of the design and construction process for an API facility can be defined in four critical steps:

1. Design
2. Procurement and construction
3. Equipment validation
4. Start-up, commissioning, and turnover

We have briefly discussed different contracting options. The API manufacturer has to decide how to procure the outside services necessary to accomplish these steps. We cannot recommend any one method as better than another. The contracting decisions must be made based on all parties' relative strengths in the execution of this type of project. If the decision is to contract out the entire process to one firm in an EPC (engineering, procurement, and construction) contract, the outside firm is expected to deliver a completed facility, validated, and ready to produce product.

The API manufacturer, with some level of in-house expertise, can elect to manage the design and construction separately. The outside design firm will be responsible for providing the proper level of documentation for a construction firm to execute the work. The API manufacturer exercises a greater level of control in this process. Also the API manufacturer will be involved in many of the decisions made in procurement of equipment and other components and be better able to influence the operability of the facility.

VII. DESIGN DEVELOPMENT

The design of a new API facility will develop from an initial "napkin" exercise to a set of documents that a constructor will use to install the new assets. Progression of the design can be inferred from the following sequences: preliminary scope, basis of design, and detailed design. Many companies in the petrochemical and chemical industries utilize this practice. Recently, this progression has been utilized in the API industry.

Development of the design is a function of process definition. Once the process is clearly identified, the API manufacturer and/or the design firm can complete the in-depth analysis of existing assets and new assets to progress the design for the project.

As previously discussed, the preliminary scope defines the major components of the API facility. The scope will have identified key processing steps, all associated equipment, and any facility requirements. The preliminary scope will be a key document in communicating to outside design firms the intent of the facility(s) and the overall process intent of the project. The API manufacturers must then decide how they want to manage critical steps of the design, construction, validation, and start-up process.

Another phase in design development currently utilized in the chemical/petrochemical industry is a "basis of design" phase. The basis of design has certain components of the design defined prior to a final cost estimate and schedule is completed. The basis of design has components such as AFD (approved-for-design) P&IDs, PFDs, and facilities definitions. The basis of design will outline permitting requirements (local government and environmental), engineering criteria for the new site (civil and infrastructure), and a preliminary project execution strategy. The basis of design represents approximately 20% of the total design.

Once the basis of design is completed and the final estimate generated, the design team will develop detailed design documents that will incorporate all the necessary information for the builder(s) to construct and start up the facility(s). The following components should be defined during this process:

- Equipment requirements
- Facilities requirements
- Utilities requirements
- Safety requirements
- cGMP requirements
- Qualification or validation plan
- Expansion capabilities
- HAZOP (hazard and operability analysis)
- Process and instrumentation diagrams (P&IDs)
- Environmental requirements (permitting)

A. Equipment

The P&IDs will identify the major equipment components to be modified or procured for the new process. It will outline the new equipment and associated controls required to run the process. The API manufacturer may have preferred suppliers of this equipment because of operability or maintenance issues. Most of the vessel and component suppliers in the industry are capable of supplying cGMP-compliant equipment. The design firm or the API manufacturer will specify the equipment to include the necessary appurtenances to make the equipment cleanable.

The design firm normally generates procurement specifications. These specifications will include definition of all major components such as materials of construction, agitator requirements, and nozzles. Major equipment for API processing is similar to that for fine chemical production and can include reactors, centrifuges, condensers, heat exchangers, distillation columns, extractors, absorptionequipment, chromatography equipment, dryers, blenders, crystallizers, and mills. These components will require validation (installation qualification/operational qualification, IQ/OQ) prior to manufacturing. It is important to have proper coordination between the design engineer and the validation team. The validation team will be responsible for generating validation protocols developed from the equipment specifications and processing parameters.

B. Facilities

Many of the recent cGMP initiatives have been focused on facility requirements. The manufacturer will be responsible for adhering to these requirements for processing, product separation, materials handling, and utilities. Because of these requirements, additional space for functions such as warehousing may be required. ICH Q7A is the document the producer will refer to for information on facilities and processing requirements. The new facility will require enough space to provide separation of raw materials (i.e., quarantined vs. approved) and for finished products and intermediates (quarantined vs. approved). The manufacturer must be able to isolate and segregate these components.

Manufacturing space containing equipment involved in critical and post-critical step processing are required to maintain a level of cGMP compliance consistent with the stage of the product. There are noticeable differences between intermediate facilities and facilities that manage final (critical and post-critical) steps of an API process.

An intermediate facility will not require the level of sophistication normally associated with a final process facility. There will be differences with respect to equipment separation, architectural finishes, utilities, and general building configuration. Some of the differences include less costly equipment separation (open bays vs. rooms), architectural finishes consistent with fine chemical manufacturing, and potable (drinking) water versus purified water.

The isolation/purification facilities will be designed with GMP considerations consistent for the final stage of the product. Some of those considerations include product isolation and separation, cleanable surfaces, purified water systems, and temperature, airflow, and humidity controls.

1. Product Separation

Product isolation is required for processing facilities involved in critical and post-critical processing. Production facilities involved in campaigning different products must be able to provide adequate separation for product isolation during transfer of product. The producer must be able to ensure the regulatory agency that all products are produced in an environment free of the potential of cross contamination. This isolation can be performed through the use of temporary barriers such as curtains or through the construction of separate bays with permanent physical barriers (walls).

Isolation for final processing steps is best accomplished through the design of individual rooms (suites). The rooms are finished with smooth, cleanable, and durable finishes such as epoxy. All utilities are piped in from adjacent mechanical rooms. All penetrations are sealed to maintain the proper environment in the process suite. The vessel heads and man ways should be kept free from overhead components that could collect dust. HVAC systems are designed to maintain positive room pressurization with respect to connecting corridors. This will protect the room from contamination by dust or other particulates. The HVAC system will have particle filtration that will filter out airborne contaminates.

2. *Utilities*

Utility requirements for API manufacturing are not atypical from fine chemical manufacturing. Process equipment will require steam, water (potable, chilled, tower/cooling), nitrogen, and vacuum. Jacket services can be designed for multiple-fluid use or for single-fluid applications, utilizing a multipurpose fluid for both heating and cooling. Buildings should be designed with utilities separated from the processing areas. Chillers, heat exchangers, pumps, etc., should be located in separate rooms, floors, or areas. Design of all process utilities are required to ensure product contact separation as outlined in ICH Q7A Section 4.

3. *Water Systems*

Water systems used in the manufacturing of APIs are subject to validation guidelines as outlined elsewhere in this book. The manufacturer will be required to utilize a water system as appropriate to the process. The United States Pharmacopeia (USP) outlines minimum specifications for various levels of water purity (2). The manufacturer will determine the quality level required at all the various stages of molecule development. The manufacturer will utilize drinking water quality, potable water, for all precritical processes (intermediate steps) and purified water for critical and post-critical applications.

Purified water systems for pharmaceutical processing require a level of sophistication not required in the production of fine chemicals. There are many different ways to generate purified water. Following is a brief description of a typical pharmaceutical grade water system. The system will include the following components:

1. Treatment
2. Sanitization
3. Storage and circulation

Treatment. The equipment required for water treatment will be determined by the quality of the incoming water. Typically, a USP pharmaceutical grade system will require pretreatment (filters), deionization, reverse osmosis, and potentially a polishing step such as continuous deionization. Many systems now incorporate ultraviolet (UV) filters for sanitization, which kill microbials and also eliminate ozone.

Sanitization. The systems are designed to be cleaned. Recent industry practices have included the use of ozone injected into the system as a sanitization step.

Other methods include steam sanitization. The ozone is then eliminated through the UV filters. The system should be designed for a complete sanitization, which includes all storage tanks and distribution piping.

Storage and circulation. Typical systems include a storage tank with sanitization capabilities. Treated water is sent to the tank and then circulated to the points of use in the manufacturing areas and returned in a continuous loop. The circulation loops are normally designed to maintain flows that will inhibit bacterial growth within the distribution systems. The system designer must be aware of the minimum velocity requirements for these systems. The designer will use a rule of 4 to 6 fps (feet per second) as a minimum velocity.

Materials of construction. The system will be constructed of sanitary materials. All fittings will be sanitary grade. These systems are built utilizing PVC or stainless steel (316L), or a combination of the two.

Other systems impacted by cGMP requirements (product contact) include nitrogen and plant air. These systems will require filtration systems to ensure no impurities are passed through and make contact with the product.

4. Safety

As previously stated, process and facilities designs are impacted by the potential need to include handling of hazardous materials including cytotoxic compounds. The newer higher potency compounds are potentially toxic in the large volumes they are produced.

HVAC systems for finishing facilities where potent/toxic compounds are handled are required to work under negative pressure. HEPA or 95% air filtration systems are utilized to remove particulate from the air stream. In intermediate processing, isolation chambers may be required to protect the facility environment. These chambers will contain the equipment that holds the material (i.e., centrifuge or dryer) and provides a physical barrier (plaster or block walls), and an air bath (under negative pressure). Operators working in this environment will be required to wear PPE (personal protective equipment). The facilities will be designed to minimize the hazard by limiting exposure to the individuals and environment.

API processing utilizes various volumes of flammable solvents. The design of the facility will require the necessary components consistent with hazardous construction. The facility will be designed and constructed as damage limiting. Electrically, most processing areas will be IEEE class 2 div. 2 construction. Architectural damage-limiting construction will include facility venting utilizing wall systems that relieve with changes to pressure in the facility. Mechanically, the processing equipment will incorporate pressure management devices such as rupture disks and pressure relief valves. Chapter 11, "Design and Operating Practices for Safety," outlines the facility requirements for hazardous conditions.

VIII. STERILE PROCESS FACILITIES DESIGN

Sterile API processing facilities are hierarchal in scope, combining many aspects of biological facilities requirements with API processing. APIs manufactured for sterile use are required to be completed (usually the isolation/purification steps) in a sterile facility. The sterile facility is designed to minimize the exposure of the product from microbial contamination.

CFR 211.42 (design and construction features) requires, in part, that aseptic processing operations be "performed within specifically defined areas of adequate size (3). There shall be separate or defined areas for the firm's operations to prevent contamination or mix-ups." Aseptic processing operations must also "include, as appropriate, an air supply filtered through high-efficiency particulate air (HEPA) filters under positive pressure," as well as systems for "monitoring environmental conditions . . ." and "maintaining any equipment used to control aseptic conditions."

Section 211.46 (ventilation, air filtration, air heating, and cooling) states, in part, that "equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product." This regulation also states "air filtration systems, including pre-filters and particulate matter air filters, shall be used when appropriate on air supplies to production areas."

The building or suite is designed with separation and control. Air quality will vary depending on the nature of the operation. The area design is based upon satisfying microbiological and particulate standards as defined by the equipment, components, and products exposed, as well as the particular operation conducted, in the given area.

There are two clean areas that are important to sterile API product quality: the critical area (class 100) and the supporting clean areas associated with it. Class 100 conditions require that air in the immediate proximity of the exposed product be of an acceptable quality with a particle count of no more than one hundred 0.5-μm particles per cubic foot of air. This is obtained by utilizing HEPA filters and laminar flow conditions with the room HVAC. Room pressurization is also critical. Class 100 rooms are required to maintain a positive pressure to surrounding rooms of at least 0.05 in. of water with the doors closed. The supporting clean rooms can vary from class 1000 to class 100,000 depending on the function with class 100,000 as the least critical to class 10,000 for adjoining rooms.

The sterile processing buildings are designed with a hierarchy of separations. Manufacturing is separate from warehousing, warehousing and manufacturing from offices and locker facilities, and also separations from utilities. Material flow is critical for a successful design of aseptic facilities. The designer should make every attempt to design the facility for unidirectional flow of components, ingredients, and product. Unidirectional flow means that materials and product all flow in one direction as the product undergoes various phases of completion. This provides the greatest assurance that sterility will not be compromised as it might in a facility that did not possess unidirectional flow.

A. Qualification Plan

The qualification plan for an API facility consists of the following:

- Commissioning
- Validation
- Installation qualifications

- Operational qualifications
- Performance qualifications

The supplier of engineering services can also provide commissioning and validation services for the API manufacturer. There are also third parties specializing in commissioning, validation, SOP (standard operating procedure) writing, and operational training. Early in the project development process (initial scope development), the contracting strategy for validation/start-up services should be determined. EPC contracts can include this as part of the suppliers' scope. The API manufacturer will have to decide how this work will be executed. The API firm can internally perform the work with engineering resources. They can use the engineering firm of record or the contractor to perform the service, or they can hire a third party specializing in validation/commissioning.

The engineering firm will be responsible for identifying key supplier documents required for validation IQ and OQ and also specifications and ranges for equipment. The validation services will develop protocols for executing each component (IQ and OQ). PQ (performance qualification) is performed after completion of OQ. The engineer or contractor will typically not be involved in PQ. Our experience has been that the producer will perform PQ on the new process.

The IQ protocols are designed to verify that the installation has been completed as specified. As an example, an IQ protocol for a vacuum pump will ensure that the right pump was installed as specified. The entire nameplate data will be recorded, documenting all necessary engineering information such as size, type, and purpose. All electrical and instrumentation contacts will be tested and verified.

The OQ protocols will test all critical parameters for the equipment. It will test all control devices, calibrate critical instruments, and test major vessels under operating conditions (pressure and vacuum).

B. HAZOP Analysis

At various stages of the design process, a hazard and operability analysis (HAZOP) must be conducted on the project. The purpose of this analysis is to identify any potential weakness in the design of a process facility. Weaknesses are identified as follows:

- Safety concerns (i.e., dangers to personnel)
- Environmental impact (i.e., chemical release)
- Economic impact (i.e., damage or loss of equipment or facility)

The HAZOP reviews will look at each detail of the process, examine what is happening in that stage of the process, and then question a series of "what-if" potential failures. Questions such as a failure of a control or loss of power will generate a list of possible reactions to that failure mode. The failure list is then generated from experience with similar process arrangements or from experience with this specific equipment. This potential failure is then analyzed and the risks are determined. A failure of low risk from safety exposure or cost of damage to the facility would not generate further action by the design team. An item with a potential of extremely unsafe condition or high cost damage would then be listed with a recommendation for additional controls or a revision to the design.

C. Expansion Capabilities

Installing expansion capabilities into a new facility should be considered by the manufacturer. Market projections for API products can vary dramatically. A recommendation for the reader is to be cognizant of the potential for expansion. When designing the new process facility or upgrading an existing plant, the API producer should position the plant to be expanded if necessary. Consideration should be made for pre-investment of some facilities or utilities during the design of the first phase. It is clearly cost-effective as compared to having to reinvest later. However, it is ultimately a management decision on managing risk. As previously mentioned, certain facility components are easily installed at one time versus staggered. A good example is piles and foundations. If the producer anticipates product growth, the scope may include the necessary subsurface components for future expansion. When the producer decides to expand some time in the future, they will already have in place the subsurface civil construction.

D. Execution Strategy and Planning

In any project, the cost and schedule predictability is important. All projects, from an office building to a major manufacturing facility, have external factors that are affected by the cost and completion of a project. When a project is first conceived, the drivers for the project establish the cost and schedule goals. If a project is purely financially driven, then cost is the major controlling factor. If speed to the market drives the project, then schedule becomes of paramount importance. In general, the project execution strategy must have a primary goal. If the project is falling behind schedule, a decision must be made to determine if the cost of overtime is justified. If cost is the driver, then a slip in schedule may be acceptable or, conversely, the cost of working overtime may be justified to maintain a critical schedule.

The "project execution strategy" must be aligned with the overall project goals. To align these goals, we must first understand how executing a project can support these goals. If cost is the main goal of a project, such as in commercial or government projects, the contracting strategy is to have competitive lump-sum bids submitted by as many general contractors as can demonstrate the financial strength to complete and be able to avoid costly foundation excavations and associated disruptions of heavy projects. This financial strength is demonstrated through the submission of a bid bond with the proposal. The quality of the end product is "industry standard."

This method of lump-sum bidding requires all the design documents be completed and the entire project construction be awarded to one general contractor. This contractor will be responsible for the procurement of the individual trade subcontracts and the procurement of all the equipment. Because the design is completed, and the basic coordination of the trades has been engineered in advance of the start of construction, the extent of extras on the project is usually limited to unknowns. Items such as subsurface conditions or, in the case of renovations, existing conditions, which are not anticipated in the design, may be uncovered during the construction activities.

The administration/management of a lump-sum general contract is also limited due to the completion of the design prior to the start of the construction activities. This project approach will take the most overall schedule time, but the final cost is easily predictable and known with great accuracy prior to the start of construction. The delivery of long-lead equipment and fabricated materials such as structural steel will often not support the overall project schedule. There will be times in the construction schedule when the project is waiting for materials and equipment to be delivered. In the construction of most API facilities, schedule is an important driver of a project. The lump-sum general contract approach will not normally satisfy the schedule requirements of the project.

Schedule time is normally reduced through a technique known as "fast-tracking." Major equipment bid packages and early construction packages (foundations, structural steel, etc.) are awarded prior to completion of the entire design. As the design progresses, other packages are released for bidding. A major component of the "project execution strategy" is the bidding strategy for the project. This system of fast tracking is normally applied to the entire execution strategy. Almost all API manufacturing projects are schedule driven.

Cost predictability for fast-track projects is less definitive. The potential exists for early construction packages to have errors or omissions that would have been uncovered if the remaining design had been complete. Whenever the design is not complete, there is cost uncertainty. Any late changes can impact design components that have already been ordered or constructed. Accordingly, the administration of a fast-track project requires extensive field effort and manpower. The number of construction contracts increases, and also the complexity of the overall project increases. Most API manufacturing companies (the project owners) do not have the in-house resources to effectively administer a fast-track project. The owners typically use resources from a construction management or engineering company to monitor field activities, procurement, cost, and schedule.

E. Procurement Strategy

There are various ways of contracting for construction and design management. An EPC, or design build contract, is the joining of the engineering design, procurement, and construction management functions with one supplier. Owners can elect to hire firms with the in-house expertise to manage all three functions, or a design firm and a construction management firm that have joined forces to provide these services under one contract umbrella. The advantage of the single contract is the single point of responsibility between the owner and the supplier.

Some owners will elect to have separate contracts with the design firm and with the construction management firm, with the construction firm responsible for the majority of the procurement. The advantage of separate contracts is that the owner retains control over the design, and the design work can start before the construction management firm is selected.

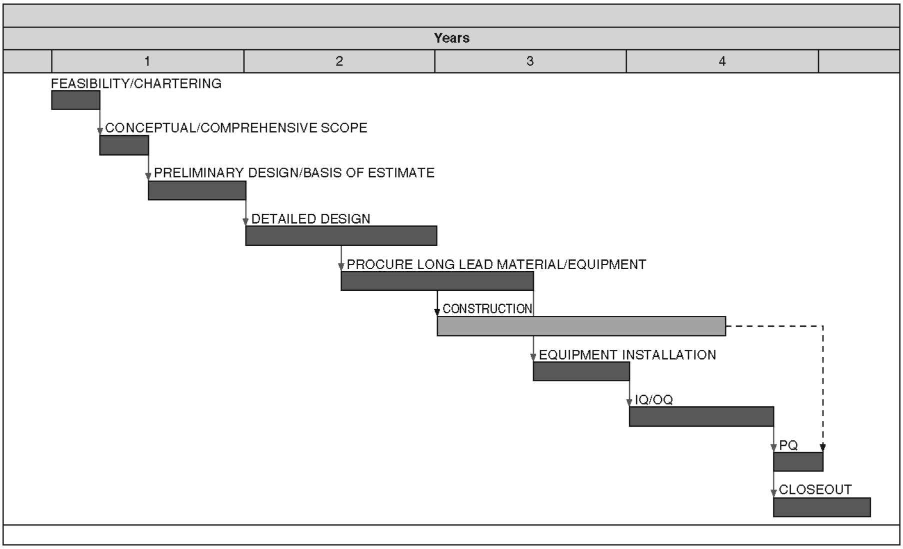
When selecting a firm to manage the design and/or construction of the project, there are a number of strategy and planning tools that these firms must use to effectively manage the overall process. During the various phases of the project, cost estimates and project schedules are prepared. These estimates and schedules are constantly refined as more details of the project are developed.

At the conceptual stage of a project, the cost estimate(s) developed is utilized for the project's overall business strategy. The initial ROI (return on investment) calculations are based on these preliminary estimates. These estimates and schedules, although based on limited data, usually not more than 10% of the total engineering, are critical to achieving the project's overall goals.

The selection of the key firms to supply the design, construction management, and estimating services is a critical early project activity. The preparation of the project estimates is usually a collaboration between the outsourced vendors and contractors who are familiar with the construction and design market and the API manufacturer (owner) who is more familiar with the chemistry or the process and the cost structure of the company.

As the design progresses, the estimate is refined. The assumptions made during the conceptual estimates must be evaluated for changes. In the initial conceptual estimate, there were constructability assumptions used to prepare the estimate, such as labor availability, equipment and material deliveries, and the sequence and methodology of the construction work. At each refinement, the level of uncertainty is reduced; therefore, the level of contingency for unknowns is also reduced. The overall contingency required for a project is in direct relationship to the level of uncertainty or predictability of the final cost of the project. In the initial stages of the project (10%), a contingency of more than 25% is common. At the completion of the detailed design, and with the process completed, the contingency should not be required at greater than 10%. In a complex process, an additional contingency is established for the final start-up and validation activities. The level of risk, which drives this contingency, is based on the complexity of the process.

When a project is "schedule driven," it is imperative that a schedule be established early in the project and be utilized during the project. During the project planning, the schedule will grow in complexity and task breakdown as the overall project is developed. The schedule must be a working plan throughout the project. This plan will be updated as new data are found and to reflect the current approach to the overall project execution. An effective schedule must have relationships between the work items. The size and the number of schedule activities on a project vary from project to project. Many computer programs exist that can arrange the schedule data in easy-to-analyze



formats. A project CPM (critical path method) schedule must have the necessary detail to show a clear critical path to be effective. The bar chart (see page 98) is the most common display of a project schedule.

A schedule can also be produced in an arrow diagram that will graphically show all the activity prior to, or depending on, an activity and subsequent activities. This presentation can be very useful in the analysis of how a project can be executed. To effectively monitor a project schedule, the level of activity should be detailed to show the items that should be accomplished during a specific period of time to maintain the overall project completion schedule. The capabilities of the design and construction management firms or EPC firm to produce and monitor an effective project schedule in the complexity required to manage these projects are an important element in the selection process of those vendors.

The selection of the A/E (architectural/engineering) and CM (construction management) firms and the contracting strategy with those firms is a function of the schedule drivers. Activities must be worked on concurrently to support the schedule. The suppliers need to provide resources for project planning, early long-lead procurement, and conceptual estimating. In many cases, the early involvement of these suppliers is contracted on a reimbursable or cost-plus basis. As the project becomes better designed and scoped, the contract between the owner and the A/E and CM suppliers can become a guaranteed maximum price, lump sum, or reimbursable contract with schedule and cost incentives. In planning the execution strategy, the resources for the start-up and validation must also be identified early in the process. Many engineering firms have the in-house resources to plan and manage the start-up and validation activities. This is also important to decide when selecting the overall procurement strategy for the project.

With an effective, realistic cost estimate and CPM schedule in hand, the manager of a project can make effective decisions regarding the planning and execution strategy. Many times marketing decisions will dictate the project completion date, which could require additional funds to accelerate the project by either working overtime or adding additional shifts. When evaluating the final schedule for an API project, the time required for the start-up and validation of the facility is critical to the success of the project. These activities usually start at the completion of construction; however, their duration and requirements make it necessary to start these activities when phases of the construction are complete. Overlapping of these activities will also reduce the overall project schedule. The early planning and strategic development of an overall project strategy will identify schedule opportunities.

The sequence of the construction can then be planned to support the validation. The development of the validation strategy should be developed as part of the overall project execution planning. The strategy for contracting for the validation services is a critical early activity. It is important to identify the process systems that affect or come in contact with the product. These systems must be validated. If chilled water or steam is used to heat the jacket of a vessel in a process, *but* that steam or chilled water never comes in contact with the final product, the utilities will not usually require validation. However, the instruments that control the steam to the vessel jacket will usually require validation. If the controls do not function properly, then the product can be overheated or overcooled. All pipe systems that transport product must be totally validated.

Another element critical to the completion of a project is the time required for testing of equipment and control systems. In project validation and procurement planning, all equipment and systems that require factory acceptance testing prior to shipment should be identified. The specifications and procurement documents should provide for the required testing and identify documentation of the testing procedure for the equipment and control systems prior to shipment to the site. In many cases, with skid-mounted equipment that often has microprocessor controllers, a significant amount of the IQ documentation and verification can be accomplished at the factory. This preplanning will save the overall project schedule. The testing, documentation, and validation activities are then accomplished in parallel with construction activities. Equipment problems are flushed out at the factory prior to the installation in the field. This pretesting at the factory can increase the productivity of the construction installation and reduce the overall project schedule.

In the development of the process automation and control system, the required testing of that control system and the factory-assembled components, and the process simulation program, must be established with the general functional specifications. In an API facility, many of the control systems perform process functions that require strict validation. The functional description for the automation system should require a complete factory acceptance test (FAT). This test should simulate the entire process and process failures and alarms. The FAT should also check and verify that the control system cabinets and controllers operate as designed. The factory acceptance testing of the process automation system prior to shipment and installation in the field is a critical step in the validation and start-up of the facility.

IX. CONSTRUCTION MANAGEMENT

As the project transitions to the construction phase of the project, the construction management plan and subcontracting strategy are developed and finalized. The subcontracting strategy is completed early in the overall construction plan. Design documents must be prepared to support the schedule of the construction activities, and the submission of vendor drawings and documents is necessary to complete the design effort. Consistent with equipment, early contracting of the process automation system will start the submission of vendor drawings to the engineer for both approval and for inclusion into the electrical and instrumentation drawings.

There are many components to the facility that may not have a long delivery, but may be critical to the completion of the various design and construction packages. Control panels, IO cabinets (the termination cabinets for the input and output wiring of instrumentation), and UPS (uninterrupted power supply) systems need accessibility, which can affect the architectural layout of support space and control rooms. Instrument details are needed from the vendors to finalize the electrical drawings and pipe fabrication drawings. Many times these smaller components will be included in the contract to be purchased by the subcontractors, rather than the API manufacturing companies (the project owners). The construction management firm and the design firm must coordinate these details to ensure that the information necessary to complete the design is passed from the vendors to the designers to support the overall project schedule.

The development of a detailed construction schedule is necessary for the coordination of the various contractors and monitoring the progress of the construction. A resource-loaded schedule for construction activities is necessary. Labor requirements must be evaluated from both the availability and the density within the construction project. A general rule of thumb is to plan on one construction worker for every 200 gross square feet of the building. In the case of compact process facilities, this can require a spot density of one worker every 150 sq ft. In the electrical and instrumentation trades, this may be as tight as one worker every 100 sq ft of gross floor space. The ability to fabricate pipe skids and systems off-site must be considered both to control labor density and to support the overall schedule goals. The construction schedule must be detailed enough to be able to show the different critical paths, but simple enough to be understandable by the various trade workers.

The construction manager's involvement during design development is critical for constructability reviews to be completed at all phases of the design. There is a constant review of how the facility will be built and whether the design is practicable. Typical questions include the following: In what sequence will the facility be constructed? Does the design allow the different trades to complete their work without blocking other trades? Any contractor who must remobilize to complete their work will add schedule to the project and cost.

Final documentation for a validated manufacturing facility is critical to the success of the project. Documentation and certification of the work is the responsibility of the construction management team. The format and items required for certification should be included in both the design documents and the validation plan. Almost all documentation provided by vendors is available in electronic format. The computer design programs used to provide this documentation should be established in the early stages of the project and validation plan. The construction manager ensures that the subcontractors and suppliers comply with these requirements. Weld documentation and instrument calibration are two of the most common certifications required of the contractors.

A. Start-up Acceptance

The start-up and operational acceptance of any process facility is a complex undertaking that requires early planning. As systems are started and functioning, they can be reviewed with the operations personnel. Training of the operations personnel for a process facility should start during the final stages of the construction. Normally, training and field start-up support is included in the purchase contracts for all major equipment and system suppliers. The training consists of classroom theory of the equipment or system, the required maintenance, and their intended functions. Classroom training should occur prior to completion of installation of equipment. The operations personnel will then be familiar with the equipment and have participated in validation of the systems.

In an API facility, the construction manager coordinates the overall construction and installation of the equipment within the process facility. The interconnecting components must be installed in a quality manner. Rework takes time and delays the entire process.

B. Prefabrication and Facility Modularization

A recent development in the industry is the use of prefabricated modules for major processing components and, in many instances, fully integrated facilities. Over time, modular design and construction has evolved from partial process assemblies that are installed within the building envelope, referred to as skids and super-skids, to full structural modules that, when combined, comprise the entire facility and internal process content. The goal for full structural modules is to maximize the off-site construction for all trades, including final finishes, so that the remaining field work is reduced to interconnections at the module boundaries and final tie-ins to local site utilities. The method of prefabrication has been used in the pharmaceutical industry quite successfully in the development of new facilities for the manufacture of sterile products, vaccines, biologics, and API finished products.

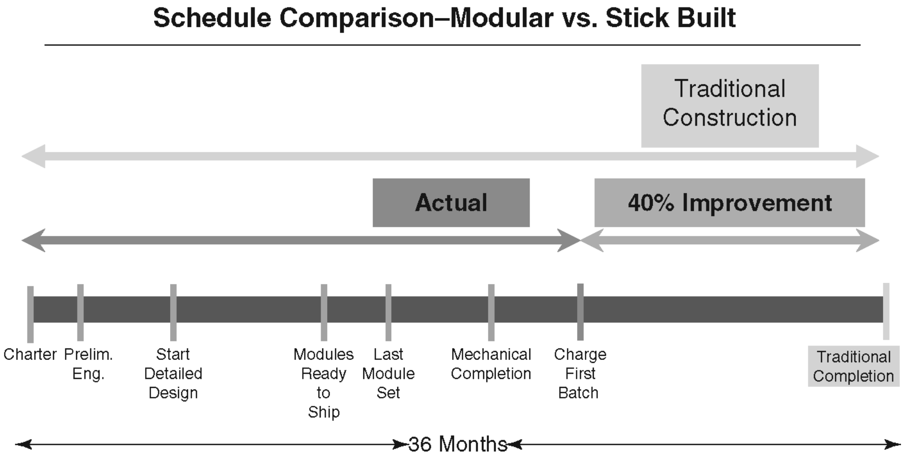
Prefabrication changes the sequence of construction. The main processing areas of the new facility are fabricated in a shop, under consistent conditions, with work occurring in parallel with site construction activities. At the completion of shop fabrication, the systems are tested and prequalified, shipped, and then field erected at the site. All of the field work associated with mechanical process systems, process utilities, HVAC, and building structure is reduced substantially. Much of the field work is connecting modules and then conducting start-up and commissioning activities.

The decision criteria for the modular method include schedule reduction, mitigation of potential labor market risks, avoiding variable and uncertain site conditions, and enhancing quality by fabricating in a controlled shop environment.

The modular method has advantages over conventional "stick" construction. The overall project schedule is reduced substantially and the owner has a finished facility in a faster period of time. A reduction in schedule of 30% to 40% is not uncommon using modularization. Variability in performance at the construction site for conditions such as weather and labor is reduced substantially and neutralized using this method. Commissioning and start-up are improved as the modular fabricator has already precommissioned systems at its manufacturing facility. Simple functions such as "bumping motors" have already been completed, usually using less-expensive factory labor in a controlled environment.

There are disadvantages to this method. Most commonly cited is cost. Fabricated modules can cost more to construct than field-built facilities. However, cash flows are improved through the shorter overall schedule and the resulting benefit of earlier production of product. Because of the shorter schedule, this method requires early design decisions. The process design team has to complete the basis of design for certain areas earlier than with a conventional design. These include early equipment selection and procurement, as well as early commitment to the final layout arrangement. Any changes once modules are in fabrication can prove very costly. Established firms using this method for the first time have experienced difficulties with the accelerated decision process required with this method. It is difficult to lock down the process. Locking down the design reduces the risk associated with changes.

Overall, the method has clear advantages over conventional stick-built construction. Time to market through reduced field construction and commissioning can be significant for a new API. The following schedule(s) shows a 12-month savings of time over conventional construction for a new process facility at an API plant.



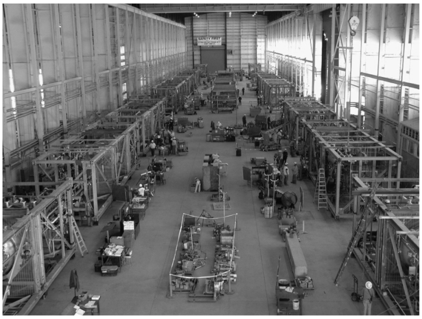
The photos on page 104 show modules of a large API expansion plant. This project incorporated 27 new modules at an existing plant, giving the facility a new API to produce at a substantially reduced schedule over conventional construction.

1. Project Turnover and IQ

The IQ of a facility is the verification that all the components within a facility that have "direct product impact" are installed correctly and in accordance with the design specifications. There must be supporting documentation that all components have been installed and that all instruments have been properly calibrated. The validation plan defines the methodology for preparing and executing the IQ. It also provides guidance with respect to IQ acceptance criteria, the use of support documentation, and responsibilities. The construction and validation team should perform a walk down of the completed system. The walk down is a review of the completed installation of the construction against the design documents. Usually, a redlined AFC (approved-for-construction) P&ID will be generated and used as documentation of the completeness of the installation. The walk down should also yield a final punch list of incomplete items.

An example of typical items that would be verified in the IQ phase of validation and in the commissioning of the remaining facility is as follows:

- Verify that the installation of the equipment complies with the design specifications.
- Verify that all required equipment, piping and electrical, and instruments are installed.
- Redlined AFC P&IDs are completed.
- Vendor documentation is available for all equipment.
- Full loop checks are completed.
- All necessary utilities are connected and ready for operation.


source: Courtesy of Jacobs Engineering

API modules in shop fabrication.

source: Courtesy of Jacobs Engineering

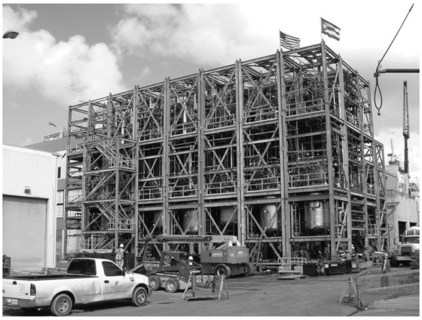
One of the reactor modules on the manufacturing floor.

source: Courtesy of Jacobs Engineering

Automation testing prior to shipment.

source: Courtesy of Jacobs Engineering

A reactor module being set at the construction site.


source: Courtesy of Jacobs Engineering

Completed API facility.

Any changes from the original P&IDs that are noted during the redlining function of IQ must be documented through a change control procedure that is detailed in the validation plan. These changes, if approved and accepted, must be incorporated into the final "as-built" documents of the facility. It is critical that the start-up, maintenance, and operations teams have complete, accurate documentation of the final as-built configuration of the facility and the process. At the completion of the construction, the construction team for maintenance and operations, and the start-up team, must assemble a "turnover package." This package will have following at a minimum:

- As-built drawings of the entire facility
- Preventive maintenance information and requirements on all equipment

- Suggested spare parts for all equipment, including delivery time and pricing
- Vendor manuals on all installed equipment

The start-up of an API facility is a challenging operation that requires early planning and a complete understanding of all the components of the facility. An operations manual with spare part and regular maintenance procedures must be in place on-site for every component in the facility. A list of spare parts required for start-up should also be assembled and these materials stored on-site for use as required during the start-up of the facility. The most critical step in developing a complete start-up plan is to develop SOPs for the facility. A complex API process facility will require SOPs to be developed on every aspect of the operation, including the maintenance procedures for the facility. The SOPs are ultimately the responsibility of the operations team for the facility, but may be developed by an engineering firm or consultant who is initially more familiar with the specific details of the facility and the equipment. An important SOP at this phase of the project is the procedure for the start-up and the methodology for shutdown procedures of the process. These procedures must show the order in which the equipment should be started and stopped, the setting of valve dampers, instruments, and controllers to avoid damage to any equipment. For the initial start-up, which is normally done with "water batching," it may be necessary to compensate for the difference in the specific gravity of water to the process when the facility is in full operation.

X. CONCLUSIONS

This chapter outlines the steps required to design and construct a new API facility:

- The business case
- Process development
- Design
- Execution strategy and planning
- Procurement strategies
- Construction management
- Validation, start-up, and project turnover

In the review of the API facilities, distinct differences between its requirements and those of a fine chemical facility exist. The product is manufactured under cGMP guidelines. There are validation requirements for the facility that document how the facility was constructed, how the facility and process will be operated, and how the facility will be maintained. In most new product introductions, the primary driver for API projects is the speed to market. The products have critical marketing considerations, and scheduling is of paramount importance, consequently, at the risk of higher cost to construct. Because of the differences in the requirements for API facilities versus fine chemical facilities, both in the construction and in the final operation, the initial planning strategy for the project is critical to the success of the project.

The design and construction professionals must be knowledgeable in the specific cGMP requirements for API facilities. The construction personnel must plan for the proper documentation of the facility throughout the construction process so that the final facility can be validated and ultimately certified to manufacture the product. The design and construction of an API manufacturing facility is a large investment of time, resources, and capital. The proper planning up front and the diligent effort to evaluate the economic options, and interface these options with an overall project schedule, will produce a facility that operates as intended and returns the predicted profit on the investment.

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5 Regulatory Affairs: Requirements and Expectations

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I. INTRODUCTION

In order to initiate and conduct clinical trials in humans, and to ultimately market a pharmaceutical product in a specific country, appropriate chemistry, manufacturing, and control (CMC) documentation must be submitted for review and approval by the regulatory authority of that country. In many countries, this CMC documentation must include appropriate information and data to assure the authority that the active pharmaceutical ingredient (API) used in the drug product is manufactured by a robust process and is well controlled to ensure safety and efficacy for the target patient population. The CMC documentation must be updated to reflect changes to the manufacture and control of the API, and frequently these changes must be formally approved by the health authority prior to administration of the material to the patient population. The review and approval of the CMC documentation can be, at the discretion of the health authority, supported by on-site or "field" inspections covering areas such as raw data review, compliance to documented internal practices and procedures, and conformance to current good manufacturing practices (cGMPs). Thus, virtually every aspect of the development, scale-up, and commercial manufacture and control of the API is subject to regulatory oversight.

While the regulatory requirements for API have been in place for some time, they are now implemented and interpreted by more and more health authorities worldwide. In addition, the overall level of API detail expected by the CMC reviewer continues to increase. Beyond the traditional purity and identity specifications, reviewers are now seeking greater assurance that the API is suitable for use in the manufacture of the specific dosage form being registered, leading to an increased emphasis on controls for both the physical properties and the physical stability of the API.

As the reader is undoubtedly aware, the first decade of the twenty-first century has been one of significant change within the pharmaceutical industry itself. Driven by increased competition within the innovator sector of the industry and by the continuing increased competition from the generic sector, all major pharmaceutical companies have focused efforts on achieving operational efficiency and ultimately reducing their cost structure. One of the most impacted areas in this regard has been the supply chain for the API. Many companies now outsource significant portions, if not all, of API synthesis, often to lower-cost manufacturers located in developing countries such as India and China. Research and development activities are also being increasingly outsourced. These trends, when coupled with the increasing worldwide regulatory emphasis placed on the manufacture and control of the API, have presented major challenges for the regulators and the industry alike.

Given the extent to which the current regulatory requirements govern development, registration, and maintenance of CMC information for the API, the preparation of accurate and complete documentation is an essential activity for a company. It is increasingly necessary that the regulatory area responsible for CMC within a company have the expertise needed to successfully register and maintain appropriate information and documentation on the API and to ensure that changing regulations are tracked, understood, and properly implemented. The advancement of information and guidance published by regulatory authorities on their Internet Web sites has greatly aided the efforts of the CMC specialist, as have the quality guidance documents developed through the International Conference on Harmonisation (ICH). This first regulatory chapter focuses on the format and general content of the API portion of the CMC documentation for both investigational and marketing authorization applications, while the second regulatory chapter covers key available guidances, including the ICH, touches on the evolving risk-based filings for APIs developed under the Quality by Design (QbD) paradigm, and looks at other recent and evolving regulatory trends and strategies.

These chapters are intended as overviews of current API expectations and are designed to guide and assist the CMC specialist in developing such filing expertise. While it is not the intent to focus only on the regulations published by the U.S. Food and Drug Administration (FDA), it is clear that in most cases, FDA requirements for API are the strictest and most comprehensive. Hence, satisfying FDA requirements often ensures that sufficient information and data exist to satisfy any worldwide regulatory agency. That said, it must also be recognized that the FDA is the leader in risk-based/QbD filing strategies, and aggressive approaches may not yet be accepted worldwide.

These chapters present an overall summary as a "snapshot in time" for an ever-evolving arena in the pharmaceutical industry, and the information contained herein is meant to supplement, not replace, the many excellent guidance documents published and maintained by regulatory authorities, worldwide, as well as the comprehensive documents published by the ICH.

The primary focus of the regulatory chapters is on conventional, low-molecular-weight APIs manufactured by chemical synthesis. It is recognized that fermentation processes and other routes are also used to manufacture APIs or API intermediates. In general, the same principles provided in these chapters will apply to these molecules, although there may be certain regulations specific to these processes that will not be covered. The regulations for biologic compounds have also been excluded here.

The chapters will focus mainly on the regulations as they apply to innovator companies seeking approval for new chemical entities. Separate but similar requirements exist for the development and maintenance of drug master files (DMFs) submitted by bulk chemical manufacturers that supply APIs to the industry [note: DMFs for APIs are generally accepted in the United States, Canada, Japan, and the European Union (EU); other countries have varying requirements regarding DMFs].

Please be aware the existing API regulations and guidelines published by the FDA and other regulatory agencies are not comprehensive and are often subject to interpretation by the company as well as the individual regulatory reviewer. It is therefore important to focus on sound scientific reasoning, supported by analytically valid data, in the preparation of original and supplemental regulatory filings. The ability to clearly communicate the science and supporting data can be a significant challenge for the CMC specialist, especially for more risk-based development programs.

II. HIGH-LEVEL REQUIREMENTS FOR SUBMISSION OF REGULATORY CMC DOCUMENTS

A. Investigational Compounds

In the 1990s and earlier, there were a number of countries in which investigational clinical trials could be conducted without the need to submit significant or even any CMC information on the experimental drug and formulation. Currently, most viable markets for early-phase clinical trials now require the submission of relevant information supporting proposed clinical trials prior to the introduction of an experimental compound into humans in their country. Generally, the investigational application document covers a specific clinical program for a desired therapeutic indication in a target patient population and must be kept current throughout the clinical development program. Modifications of the indication or target population often require a separate original investigational application.

The original investigational applications and subsequent updates are formally reviewed by the agencies. For original applications, the clinical studies may typically be initiated after a prescribed time following submission, unless the company is informed otherwise by a particular agency (e.g., clinical hold). The agency reviewers may and often do submit questions to the company based on the investigational application and should clearly communicate whether studies may proceed prior to the resolution of the issues. Frequently, guidance of expectations for the ongoing development program is provided by the agency reviewer through these questions. Formal responses on all issues should be provided to the agency in an expeditious manner (e.g., Health Canada requires responses to the "Clarifax" questions within 48 hours). Often, the responses include commitments for additional investigations as development progresses.

This investigational application document typically includes CMC information on the chemical characteristics, manufacture, control, and stability of the API and any formulations (including comparator and placebos) planned for evaluation in the clinic. For early development candidates, often a brief overview of the API synthesis and summaries of the characterization of the compound and applicable specifications (tests and acceptance limits) are sufficient to allow initiation of clinical trials. As the development program progresses and the compound is to be introduced into larger numbers of patients, more detailed supporting documentation is generally required for the API. Significant changes in the manufacture, characteristics, or controls for the API must be communicated to the regulatory agencies prior to use of the material in ongoing clinical studies through updates or amendments to the investigational application. Periodic updates documenting other, less critical changes should also be submitted during the clinical program (e.g., on an annual basis). Often, the updates to the investigational filings provide useful references for generating historical background information on the development program for inclusion in original marketing applications.

As clinical programs are being initiated in new countries throughout the world, it is essential for the regulatory specialist to learn the requirements and expectations for those markets, as well as potential implications to areas such as intellectual property protection. As an example, there are significant potential benefits from conducting clinical investigations in China, a major emerging market within the industry; however, the Chinese agency has been requiring far more data and supporting information in an investigational application than most other countries and also has a very long review time for investigational applications. Regarding intellectual property, it is clear that there are dangers providing detailed API synthesis and drug product manufacturing information to countries where patent enforcement is weak.

B. Application for Marketing

Research-oriented, innovator companies will evaluate a number of investigational compounds for potential therapeutic indications. A majority of the potential candidates do not survive the safety and efficacy studies conducted as part of the clinical development program. Those that are found to be safe and effective toward a specific indication must be registered with regulatory agencies worldwide prior to their being made available for sale in that market. The process by which compounds are submitted for approval to allow marketing is very similar throughout most of the world. Specifically, a detailed application must be submitted to the recognized regulatory authority in the country, and that authority reviews the contents and renders its acceptance or rejection of the application. In the EU, new applications are generally reviewed jointly by two member states, whose opinions govern the approval or rejection of the application throughout the EU. This EU-specific procedure will be discussed in more detail later in this work.

While the registration procedure is fairly similar worldwide, and the adoption of the Common Technical Document (CTD) has standardized the format for regulatory submissions, the content of the quality (CMC) section of the marketing application required by different countries, particularly as it relates to information on the API, varies significantly. In a number of countries, very limited, if any, information is required on the manufacture and control of the API, while in others (e.g., the United States, the EU, Canada, Israel, and Australia) very detailed information and supporting data are required on the characterization, manufacture, control, and stability of the API. A subsequent portion of this chapter covers the information supporting the API to be included in marketing applications for these concerned markets.

Following submission of the application, certain agencies will perform a high-level review or screening of its content to ensure that all basic elements are contained in the submission. Once the application is considered accepted for filing, the reviewing chemist or authority from each agency will perform a very detailed evaluation of the CMC documentation and where appropriate will provide specific questions or comments on the content of the documentation. The CMC questions often seek clarification or additional information or data on specific items or state concerns the reviewer has with the content or conclusions provided for certain aspects of the application. Often these questions are reflective of the current guidance documents published by the ICH or that agency or the current thinking of the agency on specific topics. Formal responses to each question must be provided to the agency. Timing for responses varies from country to country, but generally the rapid submission of complete responses is desirable to both the reviewer and the company. In most instances, delays in responding to the questions will result in a delay in the approval timing for the marketing application. It should be noted that knowledge of, and adherence to, the expectations documented in published agency guidelines generally minimizes the number and/or severity of chemistry questions received on a specific application. When deviating from a published guideline, a strong scientific rationale along with valid supporting data should be considered for inclusion in the application. In addition, consideration should be given to discuss major planned deviations from established guidances with the regulatory agency prior to submission of the actual application. Most major agencies are amenable to these types of discussions and have established procedures in place to schedule discussion. Generally the request is provided to the reviewer in advance via a background package, which then forms the basis for the discussion at the meeting. The company should be aware whether the opinion given at these meetings is considered binding or whether it is advisory only. Another increasingly valuable avenue for getting scientific advice on specific issues is the use of established independent consultants. This approach is often useful in markets or regions in which language is a barrier or direct contact with the agency is not readily available or when nonbinding advice is desired. It goes without saying that the competency of the consultant is critical in this scenario.

Once the concerns on all aspects of the application, including CMC, are addressed to the satisfaction of the reviewing authority, an official "action letter" is typically provided to the sponsor of the application so as to formally allow marketing of the product in that country. Sometimes, conditions for approval are stated in the letter. These conditions should be specific with respect to their impact on the marketing of the product and often must be satisfied before the product is sold. Unfortunately, in recent times final regulatory action on a marketing application has increasingly been rejection of the submission, generally due to lack of evidence of safety or efficacy. If the company elects to address the stated deficiencies, it is necessary to refile the application and restart the approval process and timeline.

In the mid- to the later part of the 1990s, procedures were established to allow for a more timely review and approval of marketing applications in both the EU and the United States. The review process to be used and the timing for approval are defined by the local regulations and are dependent on the immediate therapeutic need for the product. The EU mutual recognition procedure (MRP) and centralized procedure (CP) and the U.S. Prescription Drug User Fee Act (PDUFA) will be discussed in more detail later in this chapter.

C. Postapproval Requirements

Following approval of the marketing applications, it is necessary that the CMC information on file with each regulatory agency remain current and accurate. Unfortunately, there are a wide variety of mechanisms that must be followed in the various countries/regions to communicate changes that are required or desired post approval. The mechanisms to be used are often linked to the nature of the proposed change and its potential to impact the quality (chemical and physical) or safety of the API and, ultimately, the quality, potency, safety, or efficacy of the final drug product. Changes having a moderate to significant chance of impacting any of these characteristics generally require approval by the agency prior to the marketing of the product containing the API made or tested by the changed route. In certain markets, changes having a minimal chance of impacting these characteristics can generally be implemented (i.e., a product using the API made/tested by the changed route can be marketed), and the agencies are simultaneously or even subsequently notified of these changes via an appropriately defined mechanism.

Of critical importance in the maintenance of registered information is the existence and implementation of strong change control procedures. For the API, procedures should be in place to address changes to the manufacturing process (controls and parameters), specifications (analytical test procedures and acceptance criteria), equipment cleaning procedures, raw materials and/or their acceptance criteria, packaging, etc. These procedures should be consistent with cGMPs and are often the focus of agency inspections. Defined change control procedures should also be included as part of supply agreements with certain vendors (e.g., suppliers of key starting raw materials and packaging components), since changes made by these suppliers to information contained in the marketing application would result in the need for regulatory submissions by the application holder, which potentially could require prior agency approval.

Also of critical importance is having a clear understanding of the individual country requirements and guidelines concerning postapproval changes. The submission of a complete supplement or variation consistent with the agency expectations greatly facilitates the approval and hence the ability to implement the change. A significant discussion of this topic is included in the second regulatory chapter.

Finally, certain countries worldwide require periodic renewal of the approved marketing application, generally on a three- to five-year basis. The content of the CMC renewal documents differ significantly from country to country. Generally, these submissions are not a mechanism to submit proposed changes to the approved application; rather they are a comprehensive summary of the current approved information at the time of the renewal.

As the concept of QbD development progresses, there is a strong desire from industry and regulators alike that this approach should serve to influence the need for postapproval changes in the future.

III. CONTENTS OF REGULATORY SUBMISSIONS—API SECTIONS

At the time this text is being authored, the format of essentially all regulatory CMC submissions is driven by the CTD guidance, ICH M4. In fact, the majority of worldwide submissions utilize electronic CTD-based filings. More detail on CTD guidelines will be covered in the following chapter. The main sections required under the CTD format are consistent between investigational and marketing applications.

- S-1 General information
  - Nomenclature
  - Structure
  - General properties
- S-2 Manufacture
  - Sites of manufacture
  - Description of the manufacturing process and process controls
  - Controls on starting raw materials

  - Controls on critical steps and intermediates
  - Process validation or evaluation
  - Manufacturing process development
- S-3 Characterization
  - Elucidation of the chemical structure
  - Discussion of impurities
- S-4 Specifications for the finished API
  - Acceptance criteria
  - Test methods
  - Analytical validation data
  - Batch analysis results
  - Justification of the recommended specifications
- S-5 Reference standard
- S-6 Container/Closure system
- S-7 Stability
  - Summary and conclusions
  - Postapproval stability commitments
  - Stability data (including stress studies)

As development progresses, the level of detail contained in these sections obviously would be expected to increase as the focus of the document shifts from manufacture and testing of ongoing clinical supplies to manufacture and control of the product for ongoing market supply.

A. Content of Investigational Applications

As previously mentioned, a number of regulatory agencies, worldwide, require information on the characteristics, manufacture, control, and/or stability of any investigational API intended for experimental use in humans prior to initiation of clinical trials in their country. The information required is intended to provide the reviewer with a general background and understanding of the compound to be investigated and, generally, is considerably less detailed than that required as part of applications for formal marketing approval. Regardless of the intended reviewing agency or the stage of development for the compound, the main purpose of the investigational application is to demonstrate that the experimental API to be introduced into humans is adequately safe and is properly controlled. The exact information required in an investigational application varies from country to country and consists of all or some of the items specified in the CTD. Certain CTD sections are not appropriate at the early or even later stages of clinical development (e.g., formal process validation). In such cases, a simple statement that this information will be considered and added as development progresses is often sufficient (rather than omission of the CTD section).

The level of detail required in the CTD sections also varies significantly from country to country and is based on the stage of development for the compound. As the development program progresses, more detailed information is generally included in the investigational applications. It should be noted that investigational applications may be submitted to a number of different countries at different stages of the same development program so as to support individual clinical trials to be conducted in that country. Thus, there is a potential need to generate and maintain multiple versions of the API section of the investigational application to support the varying worldwide requirements.

For certain countries, there exist published guidance documents from the regulatory authority, describing the expected contents of the investigational application. These guidances should generally be followed when preparing an application, with any significant deviation from the guidance described and justified. For some sections of the application, the level of detail for information to be provided is not well specified in the agency regulations or guidelines; rather, experience with the respective reviewing agencies should dictate the detail provided.

The typical contents of the sections, which comprise an investigational application, follow:

1. S-1: General Information

This section should contain the full chemical name, established in accordance with a recognized nomenclature system (e.g., IUPAC); the molecular formula and molecular weight; and the stereospecific chemical structure of the API, plus any internal codes used to designate this compound within the document.

A physical description of the compound (color, form, and appearance) should be stated. A discussion should be provided on the existence of polymorphic forms, solvates, or hydrates of the molecule supported by appropriate data (e.g., thermal analyses or X-ray powder diffraction testing). Available solubility data, specific (optical) rotation values for chiral compounds, the partition (distribution) coefficient, acid/base dissociation constants, pH, and hygroscopicity data are generally also included for the selected form of the API.

2. S-2: Manufacture

The complete names and addresses are provided for all sites that have been or will be involved in the manufacture and testing of the API for use during the development program. Typically, identification of the suppliers of starting materials (i.e., compounds that impart a significant portion of the structure of the final API) and auxiliary raw materials used in the synthesis is not required.

A description of the synthesis of the API is provided. The contents of this section will vary greatly depending on the stage of the development program and the intended country to receive the application. When a compound is being prepared for early clinical trials, the process steps are generally not yet well defined and are frequently being modified or optimized. Thus, for original or early-stage investigational applications, even in some of the more sophisticated countries, it is suitable to submit a detailed flow diagram of the chemical synthesis, possibly accompanied by a brief, qualitative narrative discussion of the process steps. Only major changes to the route of synthesis should impact the filed information early in the development program, requiring an amended investigational application prior to use of the material in the clinic. As the development program progresses and the synthesis becomes better defined, additional detail is typically provided for the process description. This may occur about the time in development when the synthesis is being scaled from laboratory to pilot plant scale equipment, and the resulting material is being prepared for manufacture of the drug product lots to be used for formal stability studies (FSS). While the practices of individual companies differ, the process description provided for the manufacture of the API for use in the preparation of drug product formulations for pivotal clinical (e.g., the definitive bioavailability study) or FSS trials should be documented to a level of detail approaching that to be included in the eventual marketing application. This will facilitate comparison of the synthesis of these key developmental batches with that to be used at the final manufacturing site supplying the API for the marketed product. At this time, it may be practical to include in-process tests and acceptance criteria for key reaction steps.

Initially, little detail is required for controls on the starting materials and other raw materials used in the synthesis. As development progresses, acceptance criteria should be developed and reported for key process raw materials, particularly the starting materials. A detailed discussion related to starting material selection is included in the following chapter. Late-stage investigational applications may include acceptance criteria for all raw materials used in this synthesis.

Similarly, little information is provided for controls of critical steps or intermediates at the early phases of development, and the level of information for these areas increases as development continues and the API synthesis is better established and understood.

Typically, formal process validation data are not provided in investigational applications.

3. S-3: Characterization

Evidence supporting the structural assignment for the API is provided, typically including appropriate spectroscopic or spectrophotometric evaluations and interpretations. At the investigational stage, direct proof of stereochemical conformation (e.g., single-crystal X ray) may be provided but generally is not required.

A discussion of impurities that have been observed in development batches of the API, and to a lesser extent those that are potentially formed through the route of synthesis, is provided. The focus of the discussion is generally around reaction by-products but should also include the fate of key reagents and solvents (e.g., metals, final-step solvents), as well as known and potential degradation products of the API. The discussion should be based on the experiences from the batches made up to the time of submission, as tested by the current analytical procedures. The qualification level of the impurities as determined through safety or other appropriate studies should be addressed as this information becomes available. The understanding of impurities for an investigational compound is expected to evolve during development. Hence, early impurity discussions may be less detailed and may involve peaks for observed impurities, which are not yet structurally identified. Appropriate consideration should also be given to impurities with genotoxic potential (e.g., based on structural alerts).

4. S-4: Controls on the API

As is the case with the chemical synthesis, the analytical controls used to monitor the identity, quality, and purity of the API also evolve during the development program. Hence, there is less of a regulatory emphasis placed on those controls used in the early stages of development compared with those used in the release of material for pivotal clinical/stability trials late in the development program and eventually those used for the release of API for use in marketed product.

Early in development, there is usually a very limited database to establish meaningful acceptance criteria. Thus, the original investigational application may contain fairly broad or even tentative acceptance criteria and brief narrative descriptions of the analytical methods that make up the early API specifications for the compound. Specifications are generally included for physical appearance, assay, impurity profile, water, final-step solvents, inorganic impurities, and identity. Specific (optical) rotation should be considered for chiral compounds, and a particle size control may be applied for certain APIs, depending on the intended formulation use and their physical or chemical properties (e.g., those with low aqueous solubility). The initial assay procedure may be nonspecific (e.g., titrimetric) until a suitable reference standard is prepared and qualified.

Generally, formal method validation data need not be included in the original application, although certain country requirements and sponsor company practices may differ.

By the time the API is being manufactured for pivotal clinical/stability studies, the analytical controls and the chemical synthesis are generally well established and a larger database exists for the compound. A specific assay procedure would have typically been developed, and the impurity profile procedure would have been optimized to separate and quantitate impurities and degradation products expected from the established route of synthesis. For compounds with limited number of chiral centers, a chromatographic chiral purity procedure may be applicable, replacing the specific rotation control. The need for control of physical properties relevant to the drug product formulation should also be established, where appropriate. Acceptance criteria can be modified to reflect both process capabilities and the enhanced knowledge of the safety qualification limits for the investigational API. These better defined tests and acceptance criteria should be included in the investigational application through appropriate amendments, where necessary. In addition, validation data for the analytical test methods may also be expected by this stage in the program. The validation data should generally follow the guidelines provided in the general chapters of an applicable compendium (e.g., *United States Pharmacopeia*, *European Pharmacopoeia*, or *Japanese Pharmacopoeia*) or in the published ICH guidelines (Q2A/Q2B).

The analytical batch data section should include test results for batches of the investigational API manufactured by the route of synthesis and tested against the acceptance criteria contained in the investigational application. It is the choice of the CMC specialist, based on company practices, whether a comprehensive tabulation of data for all clinical API batches should be provided. In all cases, pertinent information such as batch size, site of manufacture, date of manufacture, and clinical use should be provided for each batch.

A discussion providing the company's rationale and justification for the proposed specifications (acceptance criteria and methods) should be included and should be consistent with the information and level of detail contained in the specific version of this section of the investigational application.

5. S-5: Reference Standard

Once a suitable reference standard for the API is established, appropriate information on its manufacture and results from characterization studies should be included in the investigational application. Often it is possible to refer to the synthetic route in the application for the preparation of the reference standard and to add any additional purification steps used. This section should also contain information on other required reference materials (e.g., an impurity standard).

6. S-6: Container/Closure System

A brief description of the primary and functional secondary materials used in the packaging of the finished developmental API should be provided (e.g., a double high-density polyethylene liner inside a fiberboard container/closure). Consideration should also be given to including appropriate acceptance criteria for the primary (i.e., product contact) material as development continues. The container/closure described in this section should be consistent with that used for stability testing of the compound, or exceptions should be noted.

7. S-7: Stability

Data from stability studies conducted on the investigational API should be presented along with the test methods used for the studies (either directly or by reference to the sect. "Controls on the API") and the conclusions reached from these studies (including the recommended storage temperature and conditions). Stability studies carried out early in development may be conducted against internal protocols and may focus on establishing suitable storage temperatures and/or container/closure systems. Typically, formal studies for long-term and accelerated stability are conducted on material made for use in pivotal clinical and/or drug product FSS trials later in the development program. Where practical, these studies should be conducted in a manner consistent with applicable guidelines published by the ICH, Q1A. This will allow data from these stability studies to be used to support preparation of the eventual marketing application. (Note: ICH Q1A does not specifically cover stability studies to support clinical trials but does cover studies to support marketing applications.)

Results from stress stability studies on the API (e.g., light, oxidative, acid, base, thermal, solution) should also be reported.

As the program progresses, certain agencies now expect that details of the stability protocol used for testing of the API be included in the investigational application.

B. Content of Marketing Applications

The marketing application is the mechanism by which the regulatory reviewing agencies in most countries will grant formal approval to sell the subject product in their market. The goals for a well-prepared API section of the application are to convince the reviewer that the compound

- is safe
- is well characterized
- is manufactured at production scale using a rugged, robust, well-controlled, and well-understood synthesis, which consistently provides material of comparable or better quality than that used in the development program
- is tested using validated analytical procedures, which show that each batch meets meaningful, justified quality requirements (acceptance criteria) reflecting

the quality of the clinical/safety material and the capabilities of the manufacturing process

- is suitable for use in the robust manufacture of the specific formulated product (e.g., has the appropriately controlled chemical and physical properties required to ensure the safety, potency, purity, and efficacy of the marketed product)
- is adequately stable, when stored under defined conditions, to ensure that its quality is maintained at least until it is used in the manufacture of the formulated drug product to be marketed

Historically, there has been a wide range of information on the API expected by worldwide regulatory agencies for inclusion in marketing applications. As stated previously, the format of the application follows the CTD guidance. In theory, the marketing application API section should be a logical extension of the late-phase investigational application, with emphasis placed on the transfer of the manufacture and testing of the API to its commercial source. The goal is to demonstrate the necessary "bridge" between the material studied in development and that to be routinely manufactured for market. In practice, however, the marketing application contains significantly more detail than even a very comprehensive late-phase investigational application, and specific versions with varying levels of detailed are tailored for submission to different markets. This area is very much dictated by individual company practices and experiences, and it would be impossible to cover all scenarios in this work. Thus, below are general practices aimed toward preparation of an acceptable API submission that meets FDA and EU requirements. Clearly there could be advantages to having a single version of the API information registered worldwide, and some companies may use this strategy. However, the level of detail required for the United States and the EU, for example, is often substantially more than that required for approval of the application in some countries. Following approval, the level of detail in the application will drive the need for postapproval supplements or variations, and hence there are definite advantages to limiting the detail, where possible.

1. S-1: General Information

Nomenclature. The recommended International Nonproprietary Name (INN), the U.S. Adopted Name (USAN), and other national names are included, if available, along with the full chemical name(s) and any internal code names or numbers for the API. Additionally, trade names for the intended formulation(s) and the Chemical Abstract Services (CAS) registry number for the API may be provided, if established.

Structure. This section will generally include a full, stereospecific chemical structure for the API, along with its molecular formula and molecular weight (relative molecular mass). If the compound is a salt or solvate, the molecular weight of the core molecule should also be provided.

General properties. The information provided for a specific compound may differ based on the exact molecule but usually includes the following information: physical appearance, thermal behavior, solubility, chirality and specific (optical) rotation, crystallinity and polymorphism, hygroscopicity, partition coefficients, solution pH, and acid/base dissociation constants. The majority of this information is generated during the early development of the compound and included in the investigational application, as discussed above. Under certain circumstances, it may be necessary to evaluate the properties of large-scale pilot batches or even early production–scale batches to demonstrate consistency with the properties reported for the early development batches. Any differences in these properties should be discussed as part of the marketing application, and sufficient evidence should be provided to demonstrate the equivalence of the pilot/production material to material used during safety and clinical trials.

2. S-2: Manufacture

Sites of manufacture. All sites involved in the manufacture and testing of the finished API and/or key process intermediates for commercial purposes are listed in the application submitted to the FDA and certain other markets, along with their complete addresses (street addresses are generally required as opposed to PO boxes). Other countries/regions focus only on the manufacturing site of the finished API, while in some markets this information is not submitted at all. According to agency practices, the sites listed in the application, including contract manufacturing and testing sites, are potential candidates for agency inspection during the approval process. Thus, the sites should be ready to manufacture or test the specified API or intermediate at the time of filing or shortly thereafter (e.g., the appropriate process equipment, quality systems, and supporting documents are in place).

If the entire API and/or key process intermediates are manufactured at contract facilities or outsourced to an independent supplier, the information required in this section differs from country to country. In the United States, the contract manufacturer/supplier for an API or intermediate is generally identified in the filing, along with specific reference to their U.S. DMF. A letter from the manufacturer, allowing FDA review of the DMF as part of the sponsor marketing application, is also needed. The use of a DMF for key process intermediates is currently only recognized in the United States and potentially Canada. In the EU and Japan, the regulations allow DMF reference only for the finished API.

Manufacturing process description. Typically, this section contains a detailed schematic flow diagram of the synthetic route to be used to manufacture the API for commercial purposes and a textual description of the processing steps. The level of detail for the synthetic process that is required by agencies differs significantly from country to country and also in some cases from reviewer to reviewer. Certain countries require no information on the manufacturing process, some will accept only a flow diagram, while others expect sufficient information such that they can understand the manufacturing route and are assured that suitable controls are in place to guarantee consistent quality batch to batch. The expectations also differ based on the type of synthetic process used (e.g., more detail would be expected for fermentation processes than for straightforward coupling reactions). The level of detail typically provided by specific companies in their marketing applications also varies greatly. The factors that impact the level of detail included in the process description are many and are often influenced by the philosophies of the individual company; hence they will not be discussed in this work.

If the API was developed using QbD principles, the process description may also indicate the established criticality of the process parameters and may include ranges reflective of the established design spaces for the parameters. Certain companies may also include their typical production operating ranges, which would be a subset of the established design space.

The process description would also generally show the point at which key in-process tests are routinely conducted. In-process testing practices are discussed further in the section "Controls on Critical Steps/Intermediates."

Controls on starting materials. Suitable analytical controls (tests and acceptance criteria) should be included in the application for all raw materials used in the filed manufacturing process description, including those defined as starting materials. The controls required for specific raw materials are dictated by the role the compounds play in the synthetic process.

Starting materials, which contribute directly to the structure of the finished API, generally require controls on identity and purity. If the synthesis utilizes more structurally complex starting materials, additional controls such as impurity limits and chiral purity testing may be appropriate. A more detailed discussion related to starting materials is part of the following regulatory chapter.

Raw materials that impact or drive the quality of the API or an intermediate (e.g., a chiral reducing agent) should have controls appropriate to their specific role in the synthesis, while reagents and most solvents may require only identity testing to ensure their suitability for use in the process.

The acceptance criteria for raw materials should be consistent with the demonstrated capabilities of the process. Evidence (experimental data) should exist that raw materials with the specified quality can be successfully processed forward. This evidence would not typically be included in the original filing but may be needed to respond to an agency question or may be reviewed during an inspection.

A brief synopsis of the test methods for raw materials is generally sufficient, and validation data have, to date, not been required in the original application. For items accepted on the basis of supplier certificates, it is still necessary in most cases to list either the company's or the supplier's tests and acceptance criteria.

Controls on critical steps/intermediates. Many regulatory agencies expect that companies will monitor quality throughout the synthetic process. Thus, they would expect in-process testing at critical steps (e.g., completeness of reaction) and/or testing of key intermediates for desired quality attributes be conducted and documented in the application. Practices and expectations for defining critical process steps and for including in-process/intermediate controls in a regulatory process description vary significantly from company to company.

Each in-process control should have a related acceptance limit that ensures successful further processing downstream. Additionally, actions to be taken if the acceptance criteria are not achieved should be included in the submission. For example, if the in-process test measures reaction completion, the actions to be taken if the desired conversion is not achieved could include further aging of the batch or charging of additional reagent.

Failure to achieve intermediate acceptance criteria should also trigger appropriate action, typically involving reprocessing of the material through the steps described in the process description or executing a rework procedure. The established rework procedures should also be included in the process description section.

In-process or intermediate testing may be used to demonstrate the removal of certain early-step impurities (e.g., reagents or solvents) or achieving appropriate quality attributes, thereby eliminating the need for direct controls applied downstream or at the finished API.

Typically, summaries rather than fully detailed in-process and intermediate test procedures are included in the application. Validation data for these methods have recently been requested by certain agencies, particularly if the results are used as a surrogate to finished API testing.

Recently, more emphasis is being placed on the use of process analytical technology (PAT) for online or in-vessel reaction monitoring. The requirements for documenting and supporting the use of PAT are generally similar to those for more traditional in-process testing.

Process validation/evaluation. Presentation of information in this section of the CTD is a relatively new requirement and is being actively defined by various agencies at this time. The requirements may be different depending on the nature of the API synthesis and the end use of the API (e.g., formal process validation data may be required for the sterility operations for sterile APIs). Consultation of appropriate guidance documents, when available, is therefore recommended.

Process development history. For traditional (non-QbD based) programs, a brief discussion of the development of the synthetic process may be appropriate in the marketing applications. This section allows the company to establish the bridge from the synthesis used to manufacture early-development safety samples, clinical materials, pivotal clinical/stability batches, and the API for a commercial product. This bridge is particular valuable for reviewers in the more sophisticated markets who may not have previously reviewed the processes contained in the investigational applications. Again, the level of detail provided for this section will vary considerably.

For APIs developed using QbD principles, this section of the application is the logical place to document and justify the QbD strategy and conclusions and to present the appropriate supporting data. The complexity of this presentation will no doubt vary on the basis of the level of QbD used. The goals would be to present the key aspects of the risk assessment that drove the development, to clearly demonstrate the applicable process knowledge gained during development, and to show the mechanism used to assess criticality and establish design spaces. The assessment of criticality for process parameters and quality attributes should be linked, as appropriate, to the drug product formulation and ultimately to patient needs.

Particularly for QbD-developed APIs, it may also be appropriate to include a discussion of the overall "control strategy" for the API, which will be discussed further in the second regulatory chapter.

A "mock" QbD development example is currently being generated by the European Federation of Pharmaceutical Industries and Associations (EFPIA), and in the future this document may provide a solid example to be followed in authoring this "Process Development" section.

3. S-3: Characterization

Elucidation of the chemical structure. Data are required to support the structural assignment for the API made by the process described in the marketing application. Typically, data are generated using appropriate spectroscopic or spectrophotometric techniques. Interpretations of the data (e.g., assignment of spectral bands or signals) are also included. Additionally, results from a study (e.g., single-crystal X ray) proving the stereochemical conformation of the molecule should be provided. Recently, certain agencies have also been requesting evidence of the chemical structure of starting materials, process intermediates, and key synthetic impurities.

Discussion of impurities. The contents of this section should be suitable to demonstrate to a reviewer that the company understands the origins of, and has in place adequate controls for, impurities that may be present in the API made by the filed process, with a focus on those impurities actually present in batches produced during the development program. The discussion should demonstrate that the controls in the application are consistent with qualified levels of impurities (e.g., through safety studies) and with the ICH guidance document, Q3A, particularly with respect to the specified, dose-dependent identification and qualification thresholds. The level of detail required to achieve these objectives varies depending on the complexity of the synthesis. As with the process description and process history discussions, the detail of this section is often driven by internal company philosophies. Regardless of the level of detail, the discussion should include structurally related impurities derived from the route of synthesis, process solvents, reagents and their by-products (e.g., inorganic impurities), and potential degradation products. For chiral compounds, potential isomers should also be addressed. Typically, the chemical structure and a brief discussion of the formation or origin of the impurity are given. The fate of the impurity in further processing is also included, along with the levels observed in actual batches. This section should mention where the impurity is routinely controlled in the synthesis (e.g., in the starting material, in a subsequent intermediate, or in the finished API). A discussion of the methods used to monitor these impurities may be provided or referenced. For impurities that are not directly controlled through the finished API specifications, justification for omission of a direct control may be provided in this section or in the section "Justification of the Recommended Specifications."

4. S-4: Specifications for the Finished API

Acceptance criteria. A listing of the acceptance criteria to be used for release of the finished API is required. These limits should be developed according to established practices within the individual company, taking into account the demonstrated process capability (batch data) and safety/toxicity data for the compound and its potential impurities. The guidance documents available from the ICH and from various regulatory agencies should be considered during the development of the acceptance criteria for the API.

Test methods. The analytical procedures used to test the finished API should be provided in the application. The level of detail is again subject to company philosophy; however, sufficient detail should be included to provide the reviewer with a solid understanding of the method. In certain countries, the test methods may actually be run in an agency or contract laboratory so as to confirm results on samples provided with the application. Certain tests can be performed using established compendial methods, with the compendial methods referenced in the application. Often it is helpful to attach copies of these compendial methods to the application to facilitate review, particularly in countries that do not follow the referenced compendia.

Analytical validation data. Complete validation data are required showing the analytical methods to be suitable for their intended use. Several guidances are available on analytical method validation, including the *United States Pharmacopeia* General Chapter <1225>, *Validation of Compendial Methods*, and the ICH guidance documents *Q2A—Validation of Analytical Methods: Definitions and Terminology* and *Q2B—Note for Guidance on Validation of Analytical Procedures: Methodology*. Following these or similar guidance documents should ensure suitable validation data in the regulatory application. For tests that reference established compendial methods, revalidation of the procedure is generally not required; however, it may be necessary to demonstrate that the methods can be suitably applied to the subject API. For impurity methods, the validation data (e.g., response linearity, method sensitivity, and limits of detection and quantitation) should be consistent with the acceptance criteria recommended in the application.

Batch analysis results. Complete batch analysis data should be included for key batches prepared throughout the development program, including, if practical, material manufactured at the site(s) that will supply material for commercial purposes. These test results should be provided against the specifications in place at the time of the release of the batch for its intended use. Often, it is valuable to include retrospective analyses of key batches using techniques established or modified subsequent to their initial release. This could be particularly beneficial for impurities, assuming the impurity profile methods were modified during development. It is also expected that information on the manufacture (date, size, location) and use of each listed batch (clinical, safety, stability, market product, etc.) be included in the application.

Justification of the recommended specifications. It is often helpful to present the rationale used for establishing the acceptance criteria proposed for the API in the marketing application. This will provide the reviewers with an understanding of the thought processes used to establish the controls (e.g., are impurity limits based on safety/toxicity studies, analytical results, or both? Were ICH guidances followed? Which batches were used to set acceptance criteria? Were limits determined statistically?). Also, this section can be utilized to support the decision to omit certain direct controls on the API. Providing this information does not ensure acceptance of the proposed specifications by all reviewers; however, it may help to focus reviewer comments related to the recommended acceptance criteria.

5. S-5: Reference Standard

Method of preparation. The preparation of the primary reference standard for the API should be provided with a focus on the means of purification of the material. The synthesis used to manufacture the batch can be summarized, or referenced, to another section of the application, as appropriate.

Characterization data. Full characterization data should be supplied for the primary reference standard, including the results from analytical testing and spectral characterization. The assigned purity of the reference standard should be clearly designated.

If more than one reference standard lot has been made during the development program, and subsequent lots are characterized against the original reference standard, it may be appropriate to provide information on the manufacture and characterization of the original lot in the application. If the reference standard differs from the API (e.g., a more stable salt form or a solution is used), this should be indicated and the rationale provided. Information should also be provided for all other standard materials cited in the application, including, for example, those used to establish chromatographic system suitability and those used for analysis of starting materials, impurities, or intermediates.

6. S-6: Container/Closure System

A description and statement of the composition of the container/closure system used to store and/or ship the finished API should be provided. Where a nonroutine system is used, a drawing is often very useful. Although the requirements differ, it may also be appropriate to discuss any controls in place for acceptance, particularly of the primary (product contact) components, and possibly the cleaning of the container closure system.

7. S-7: Stability

Summary and conclusions. A summary should be provided describing how the stability characteristics of the API were determined during the development program. The discussion should include a review of the stability-indicating test methods used in the studies, the batches tested, the storage conditions and containers evaluated, and the final recommended storage conditions for production material. A shelf life or retest period should be proposed on the basis of analysis of the available data at the time of submission. Testing generally includes both long-term and accelerated studies, using the conditions described in the ICH guidance document *Q1A—Stability Testing Guidelines: Stability Testing of New Drug Substances and Products*. Additionally, stress studies exposing the compound to acid, base, high temperature, light, and oxidation should be reported (these studies may be performed as part of the validation of the impurity profile method so as to demonstrate selectivity as well as the stability-indicating nature of the method). Solution stability studies may also be performed and reported. The batches used to establish shelf life or retest dating for the API should have been manufactured minimally at pilot scale using a synthesis equivalent to that to be used for preparation of material for commercial purposes.

Postapproval stability commitments. Agencies expect that companies will have in place a procedure for routine monitoring of the stability characteristics of API production material. Recently, several agencies have required that the post-approval API stability protocol be provided in the marketing application. The nature of the commitment contained in the API stability protocol will vary on the basis of the stability characteristics of the material and the practices of the individual sponsor company.

Stability data. Tabulations containing the actual test results from the studies summarized in the stability section of the application should be provided. These results should support the conclusions stated in the document. Any deviations from the recommended acceptance criteria should be noted and explained. Data from stress studies can often be referenced to the analytical methods validation section of the application or vice versa.

C. Other Documentation Included in Marketing Applications

The CTD format allows other region-specific information to be provided in a separate section of the application. The requirements for this section are often described in detail in the individual agency guidance documents. The CTD format also specifies sections for inclusion of references and attachments, as appropriate. Additionally, the CTD includes a quality overall summary (QOS) of the more detailed information provided in the application. This QOS may be used during the review of the application by other reviewing disciplines (e.g., clinical and pharmacological/toxicological).

D. Drug Master Files

It should be noted that the filing requirements also apply for APIs purchased from a contract manufacturer or supplier. A significant portion of the CMC information in this case may be provided through reference to a DMF, where the regulations allow (e.g., the United States, EU, Canada, Japan). The DMF serves as a mechanism by which the API supplier can protect intellectual property such as the exact manufacturing route. In the EU, intellectual property is included in the "closed" portion of the DMF, which is submitted directly to the reviewing agency and is not shared even with the marketing applicant. The remainder of the API information is provided in the "open" portion of the DMF and is provided to the agency both via the DMF submission and directly in Section S of the marketing application. In the United States, a full DMF is provided to FDA by the API supplier, along with a letter providing the agency the authority to review the DMF information on behalf of the NDA sponsor. Part S of the NDA would contain certain key information on the API, for example, the sponsor's acceptance testing requirements.

In the United States, it is also possible to support complex API intermediates that are purchased from outside sources using the DMF mechanism. Currently, this practice is not used in other markets; thus the information for the intermediate would need to be included directly in the sponsor's application.

IV. REGISTRATION SAMPLES

Samples of the API, reference standards, and key impurities will be requested by certain agencies so that they can perform the test methods contained in the marketing application. These samples plus certificates of analysis, and sometimes the analytical columns and reagents required for testing, are often sent to the reviewing agency or their designated testing laboratory shortly after submission of the marketing application. The exact quantities required are driven by the test procedures. In the United States, samples of the API are also required for retention as forensic samples.

V. THE REVIEW AND APPROVAL PROCESS

The period of time during which the regulatory agencies are reviewing the contents of the marketing application can be very dynamic, visible, and sometimes intense. Since the goal of the company is to get the product to market in each country in the fastest period possible, there will undoubtedly be pressure for each individual discipline to reach an agreement with their reviewers on the final content of their respective sections of the application. This will often require negotiation, clarification, additional information/data, or more detail to address the concerns of the reviewer. Frequently, compromises must be reached. Occasionally, the company must accept undesired decisions by the reviewer in order to gain approval. For the API section of the application, the critical discussions often will focus on the specifications applied to the finished API. Obviously, it is important that meaningful and justifiable test methods and acceptance criteria be approved and that the manufacturing process be capable of routinely producing material that meets these controls.

A definite strategy should be established for developing responses to agency reviewer questions. It is important that responses be well thought through, provide answers to specific questions, be based on a sound scientific rationale and data, and not provide excessive additional information that may prompt further agency questions or concerns. It is also important that the responses be consistent with the information and data contained in other sections of the application. It may be appropriate to seek clarification of the questions from the reviewer, particularly in cases where the questions are translated from another language. Since agency questions on the initial application could potentially be received from a large number of countries over a fairly extended period of time (depending on how the submissions are rolled out by the company), it is also necessary to ensure that changes made for one country do not contradict or impact the content of the application in the other countries.

While the path of least resistance during the approval process could be to agree with the reviewer comments and recommendations, this approach frequently does not best serve the interest of the company. It is often well worth the effort to defend the original recommendations or conclusions in the application or to seek a reasonable compromise position. It may be necessary to establish direct dialogue with the reviewer, if possible, to avoid prolonged discussions on a problematic issue.

Questions from regulatory agency reviewers are valuable learning tools and often aid the company in the preparation of future applications for a particular market or markets. This learning should be communicated back to the development areas, as much of the content of the application has its origins in early development.

Finally, it is critical to keep appropriate impacted areas (e.g., manufacturing and testing sites and raw material purchasing areas) within and outside the company aware of the ongoing discussions and the final outcome of the review and approval process. Impacted areas should be directly involved in the preparation, or at least review, of regulatory responses and commitments.

It is well recognized by industry and regulatory agencies alike that review and approval of the application has the potential to be a long and difficult process, which could delay availability of necessary medicines to the patient. In the United States and EU, regulations have been enacted that seek to limit the duration of the majority of regulatory reviews, provided the information contained in the application meets minimum standards of completeness and acceptability.

The United States adopted a process known as the PDUFA, which defines the expected length of time for review of an original application. In exchange for a fee, the FDA agrees to render a decision on the application within a period that is dictated by the public need for the new drug product. Currently, decisions on applications serving major therapeutic needs (1P compounds) will be targeted for 6 months. Other applications accepted under the PDUFA should be reviewed within a 10-month period. Since the timeline is aggressive from an agency prospective, there is more pressure on the sponsor to provide a clear, complete, and accurate original application, to be ready for preapproval inspections (PAIs) of facilities contained in the application, and to rapidly achieve resolution of issues raised during the review. This may be increasingly critical for filings based on QbD, which are generally more complex, data-rich submissions that could require additional time for the agency to review and understand.

In the EU, marketing applications for new products must now be submitted for approval through one of two processes, the CP or the MRP. Under both procedures, the original application is initially reviewed by one or two of the EU member states. Under the CP, two initial reviewing countries (rapporteur and a co-rapporteur) are selected by the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMEA). The rapporteur and co-rapporteur perform independent assessments of the application and work with the sponsor to address any deficiencies in the application. These assessments are then reviewed by the remaining EU member states. The procedure is governed by very specific timelines established by the EMEA. These timelines directly impact activities of both the reviewer and the sponsor company, and deviations from the timing by the sponsor (e.g., delays in responding to agency questions) will impact the timing for approval of the application. Currently, the CP process is targeted for a decision on the application in 210 days.

The MRP involves the applicant selecting a reference member state (RMS) for initial review of the application. This review process is less structured in the EU guidelines, and timing may vary depending on the selected RMS and the complexity of the application. The RMS will generally issue incomplete letters during its review, seeking additional information to support its approval of the application. Once the application is approved by the RMS, the applicant generally will update the documentation to reflect the outcome of the approval process (e.g., the CMC documents may require updating to reflect updated or additional information or controls). At the same time, the RMS prepares assessment reports to be shared with the remaining EU member states. The application is then submitted for mutual recognition to some or all remaining EU concerned member states, which involves a defined 90-day review period. Timing for comments/questions, company responses, discussions, and final action are well defined and quite aggressive. Under the MRP, responses to all issues raised by the EU member states must be submitted within 7 days of receipt of the questions, which occurs approximately 2 months following initiation of the process. The final decision on the application (approval, company withdrawal of the application in some or all member states, or binding arbitration) is then made by day 90.

VI. PREAPPROVAL INSPECTIONS

With the recent advent of regulatory agency site inspections during the approval process for marketing applications, an increased emphasis must be placed on the readiness of the site to manufacture and test the specified API or process intermediate. In particular, compliance to cGMPs and current good laboratory practices (cGLPs) must be ensured, and supporting data must be available and in good order to substantiate the information submitted in the application. Inspections may occur at any time following submission of the application but usually will not be initiated until the application has been judged to be acceptable for review by the agency. The exact timing for the inspection may be negotiated, and its duration will depend on the extent of information to be covered and the observations made.

Most companies will attempt to ensure site readiness through audits of internal and contract facilities prior to submission of the filing. Sites specified in the application should have manufactured the API or intermediate at the time of filing or at least be suitably equipped and prepared to do so. All process (e.g., master batch records) and control (e.g., analytical quality standards) documentation should be completed and approved. Appropriate standard operating procedures (SOPs), equipment qualification and cleaning documentation, and employee training records should be in order and available for inspection.

The importance of a successful inspection cannot be overstated, as significant concerns uncovered during a PAI can delay and even prevent approval of the application. Deficiencies may also be considered indicative of deeper problems within the company and may have an impact beyond the subject filing.

VII. POSTAPPROVAL CHANGE EVALUATIONS

Interactions between the company and the regulatory agencies do not end with the approval of the marketing application. In fact, most agencies place as much emphasis on postapproval activities as they do on approval of the original filing. The reason for this practice is simple—the agencies are charged with ensuring the drugs being marketed in their country are and remain safe and effective. Thus, changes to the information approved in the marketing application must be reviewed with, or at least communicate to, the respective agencies, often before the drug product containing the API made or tested under the change can be placed on the market.

Countries have very different requirements regarding filings to support a planned process or analytical change, involving different filing categories and data and documentation needs. To further complicate matters, these requirements are actively being reassessed and updated in a number of major markets as this work is being authored. Certain key available guidance documents will be discussed in more detail in the following chapter. The need to file process changes is often directly related to the level of detail submitted in the marketing application. Certain minor changes can often be made with minimal regulatory impact (e.g., via a U.S. annual report or by agency notification), while more significant changes generally require formal agency approval.

For all postapproval supplements/variations worldwide, the key for the company is to provide data-driven evidence that the intended change does not adversely impact the quality (e.g., impurity profile, physical properties) of the API. It is often sufficient to demonstrate comparability of pre- and postchange material, provided adequate analytical procedures exist to do so. Where this comparability is not achieved, it is necessary to show conclusively that the change does not impact drug product safety, quality, or efficacy, based on either performance tests on the resulting drug product or repeat of trials to show bioequivalence to prechange material.

While the FDA supports the demonstration of comparability at the impacted point of the synthesis or at an appropriate subsequent intermediate (as discussed in the following chapter), all other countries require comparability data on the finished API, produced minimally at pilot scale, and in some cases on the finished drug product. Some countries also require stability data on the API and possibly the drug product in support of the more complex proposed changes. Thus, timing for filing of changes to the API synthesis is something that must be appropriately considered. Since a drug product made with the process change material often cannot be released for sale to a market until approval of the change is obtained in that market, the requirement to produce a full-scale API and especially drug product batches coupled with prolonged approval processes tends to have negative business implications for a company. Thus, changes requiring prior agency approval are generally undertaken only for need or significant long-term benefits (e.g., financial savings).

One mechanism available in the United States to potentially minimize the adverse business impact caused by review and approval timing for certain postapproval changes is the comparability protocol. A sponsor is allowed to file a prior approval supplement, for a specific planned change, containing a description of the nature of the change and the data and acceptance criteria that will be generated to clearly demonstrate comparability of the change material to that made by the current process. The FDA will review and approve, if appropriate, the comparability protocol, allowing the sponsor to then submit the supporting data consistent with the protocol via a changes-being-effected (CBE-0 or CBE-30) filing. The concept of the comparability protocol is being assessed by other regulatory authorities and may evolve into a meaningful strategy to reduce the delay between actual manufacture of the API under a process change and the ability to sell a product containing that material in the specific country.

Another tool recently introduced in the EU to facilitate more efficient postapproval change control is the Certificate of Suitability (CoS). Obtaining a CoS involves the review and approval by the European Pharmacopoeial Commission of the current API characterization, manufacturing, and control data for an already-registered API. The commission then grants the CoS, which can be referenced in existing marketing applications, replacing the API section of that application. The CoS must be maintained, and therefore changes made to the API must be filed to the CoS. At this time, the EU only recommends the use of a CoS for established APIs; however, legislation has been proposed that would mandate this approach for APIs that have monographs in the *European Pharmacopoeia*.

6

Regulatory Affairs: Guidelines, Evolving Strategies, and Issues

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I. INTRODUCTION

The intent of the preceding chapter was to briefly outline the requirements and general expectations related to the active pharmaceutical ingredient (API) for submitting and maintaining the Chemistry, Manufacturing, and Control (CMC) sections of both investigational and marketing applications. I hope this work adequately conveys the importance of this activity to a company, as well as the complexities for both the company and the reviewing agencies. This chapter will focus on tools and strategies that are available to support this critical function. Much of the information will be shared through Web links to appropriate sites containing the actual guidance documents. These links are accurate as of the authoring of this chapter in early 2009.

II. GUIDELINES ISSUED BY THE INTERNATIONAL CONFERENCE ON HARMONISATION

Any discussion of current regulatory guidelines applicable to the pharmaceutical industry must begin with the outstanding progress made by the International Conference on Harmonisation (ICH). The ICH was initiated in 1990 in order to bring an increased degree of consistency to requirements related to pharmaceutical products in the European Union (EU), the U.S., and Japanese markets. The origins and goals of the ICH are well summarized in the document at http://www.ich.org/cache/html/355-272-1.html. The ICH contains both regulatory and industry representation from these three major markets and provides a forum for direct discussions to achieve strong standards and guidelines. Recently, other countries have been added as formal observers to the ICH process, increasing its scope and acceptance worldwide.

The process used by the ICH to prepare regulatory guidance involves a timeline-driven, multistep process (see http://www.ich.org/cache/html/2830-272-1.html for a complete description) beginning with the official charter of an expert working team consisting of industry and regulatory members with the appropriate background and expertise on the proposed subject matter. The working team will draft a document for internal team review and then will update the draft and post it for public comment [in the United States, the Food and Drug Administration (FDA) would publish the draft in the Federal Register]. At this time, many interested companies or industry groups [e.g., PhRMA, the European Federation of Pharmaceutical Industries and Associations (EFPIA)] will frequently provide comments on this draft version of the document. The comments are reviewed by the working team, and assuming there are no major content changes required based on these comments, the guidance then proceeds to final approval and implementation. Once finalized, the existing documents are periodically reviewed and revised, as appropriate.

Two major efforts undertaken by the ICH are discussed below, the Common Technical Document (CTD) for quality submissions and the ICH-Quality guidance documents, with a focus on those documents impacting the API.

A. ICH M4—Common Technical Document for Registration of Pharmaceuticals for Human Use

A major goal for the ICH was to standardize the presentation of scientific information and data required to register pharmaceutical products in the member countries. Such was the genesis of ICH M4, the CTD. Ideally, the CTD would dictate a single version of the necessary documentation that would be appropriate for submission in each of the three ICH participants, and that could eventually become the worldwide standard for regulatory submissions. Looking at the CTD for the Quality (CTD-Q) section of the submission today, it is clear that the ICH fell just short of this desired outcome. The CTD-Q did successfully establish a uniform format that is essentially accepted worldwide, and it did provide a high-level overview of the type of information that should be included in the application. Unfortunately, consensus was never achieved on the specific information to be included in each section or the level of detail that would be required by the agency reviewers. Recognizing that full content harmonization would be difficult, the ICH established the R section of the document for regional specific information. Even with the R section supplementing the API (S) and drug product (P) sections of the application, today many companies still prepare and maintain separate versions of the CTD-Q documentation specific to different countries or regions of the world. Despite this limitation, CTD-Q has been a very valuable guidance for industry and regulators.

A copy of the current version of ICH M4: CTD-Q, in HyperText Markup Language (HTML) format, can be obtained from the link http://www.fda.gov/cder/guidance/4539Q.htm. The current version was issued in final form in August 2001. A CTD submission consists of five modules, three of which have quality components.

Module 1 is intended for region-specific information, including application forms and proposed labels. Japan also uses this module to document the degree of criticality for all parameters in the API and drug product process descriptions, and this designation of criticality dictates the requirements for postapproval changes impacting those parameters.

Module 2 is intended as a general introduction to the pharmaceutical product that is the subject of the application and to provide a comprehensive summary of the various sections of the application. A Quality Overall Summary (QOS) is required in Module 2. As stated in the preceding chapter, the QOS may be used as an information resource for reviewers of the other disciplines of the application. A well-prepared QOS also has potential utility for the chemistry reviewer, allowing that reviewer to efficiently gain an overview of the contents of the CTD-Q sections and focus his or her attention on certain key areas within the full submission. In this regard, the QOS would serve a similar purpose to the former EU Expert Report and Summary Tables or Japanese Gaiyo documents. At this time, there is no consistent guidance on the preparation or contents of a meaningful QOS, and hence practices in the industry differ significantly. Some sponsors will follow the principles for the EU Expert Summary or Gaiyo, while others will essentially duplicate the full Module 3 information as the QOS.

Module 3 is intended as the repository for the complete, detailed version of the CMC documentation, and its preparation was reviewed in the preceding chapter.

It should be noted that recently, certain regulatory agencies, including the U.S. FDA, have moved to requiring electronic submissions of the investigational and marketing applications in CTD format (eCTD). A very comprehensive guidance on eCTD is available as ICH M2, which can be found along with other valuable CTD documents on the FDA guidance page [http://www.fda.gov/cder/guidance/index.htm#International%20Conference%20on%20Harmonization%20-%20%20%20Joint%20Safety/Efficacy%20(Multidisciplinary)].

B. ICH-Quality Guidance Documents

As of the preparation of this chapter, the ICH has published and finalized Quality/CMC guidance documents up to and including ICH Q-9: Quality Risk Management. Two significant new guidances are in the preparation phase, namely, ICH Q-10: Pharmaceutical Quality System and ICH Q-11: Development and Manufacture of Drug Substances. Many of the ICH-Q topics have resulted in multiple guidance documents (e.g., there have been six documents related to various stability topics, designated as ICH Q1A through Q1F). In all, more than 25 comprehensive guidance documents applicable to individual quality-related disciplines are presently in final form. Many of the guidances have been revised since their original issuance so as to remain consistent with current issues and thinking, and only one has been formally withdrawn (ICH Q1F). A comprehensive list of the currently available ICH guidance documents in the quality discipline is available through the following FDA guidance page: http://www.fda.gov/cder/guidance/index.htm#International%20Conference%20on%20Harmonisation-Quality.

The current guidance documents with direct API impact focus on stability (Q1A, B, E), analytical methods validation (Q2A, B), impurities (Q3A,C), text for use in the pharmacopoeia (Q4B), specifications (Q6A), good manufacturing practices (GMPs) (Q7A), quality risk management (Q9), and quality systems (Q10, presently in draft). While Q8 provides guidance for development of the pharmaceutical dosage form, its contents have also been applied to API development under the Quality by Design (QbD) paradigm. As previously mentioned, a specific guidance on API development has been chartered as ICH Q11. The high-level, API-relevant content of these guidance documents follow.

C. Q1A(R2)—Stability Testing of New Drug Substances and Products

This document provides detailed guidance on data to be provided in the marketing application to support the stability of the API. Recommendations are provided on the number and nature of the batches to be tested, the testing that should be conducted, the testing intervals, and the contents of a stability commitment for production material.

D. Q1B—Photostability Testing of New Drug Substances and Products

For an API, this document recommends both forced degradation and confirmatory photostability testing. Information related to light sources, the method of sample preparation and analysis, and interpretation of the results is provided.

E. Q1E—Evaluation of Stability Data

This guidance provides recommendations for presentation of API stability data in the marketing application, as well as a detailed discussion of evaluation and extrapolation of the data in order to establish the proposed retest date for the API. Separate guidance is presented for the API stored at room temperature and below room temperature. In addition, significant discussion is included on the statistical evaluation of stability data.

F. Q2A—Text on Validation of Analytical Procedures

This guidance states the API test methods that should be validated and provides the data elements that should be included in the validation. Also, conditions are mentioned that could drive revalidation.

G. Q2B—Validation of Analytical Procedures: Methodology

Q2B complements Q2A as a "how to" guide for analytical validation. Recommendations are provided for executing studies related to each data element contained in Q2A.

H. Q3A—Impurities in New Dug Substances

Q3A is considered one of the most valuable guidance documents prepared to date by the ICH and has become a worldwide standard for managing impurities in APIs. The document includes a classification of the type of impurities covered in the guidance. Detailed considerations are then provided for:

- The rationale for reporting and controlling the various classes of impurities
- The appropriate analytical methods to be used
- The method of reporting impurity values of tested batches in the application
- The method of listing impurities in the recommended API specifications
- Impurity qualification and identification criteria

The decision tree for qualification and identification of impurities is of particular value, as it provides very clear, universally accepted expectations for this key developmental activity. The detailed glossary contained in Q3A is also extremely useful in standardizing the terminology that is used in preparation of the marketing applications.

I. Q3C—Impurities: Residual Solvents

This document expands on the guidance contained in Q3A, specifically addressing residual levels of solvents used in the API synthesis. The guidance is a risk-based approach based on the toxic potential of the solvent. Recommendations are provided for testing and establishing acceptance limits for solvents designated as class 1 (those to be avoided), class 2 (those to be limited), and class 3 (those with low toxic potential). Acceptance limits appropriate for class 1 solvents are specified. Two options are provided for establishing limits for class 2 solvents—conformance to published concentration limits and conformance to calculated Patient Daily Exposure (PDE) limits. Recommendations are also provided related to the test methodology to be used and the reporting of solvent data in the application. The document references a companion guidance, Q3A – Tables and List, which contains a list of commonly used solvents and provides their classification. For class 1 and class 2 solvents, the current acceptance limits (concentration and PDE for class 2) are given.

J. Q4B—Evaluation and Recommendations of Pharmacopoeial Text for Use in the ICH Regions

This guidance is specifically developed to facilitate the recognition by regulatory agencies of selected text in the pharmacopoeia. The API-related topic covered to date is "Residue on Ignition/Sulphated Ash."

K. Q6A—Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

Q6A contains guidance on a number of practices and expectations related to development of controls for the API. General information is provided on a number of non-traditional testing approaches (e.g., skip testing, parametric release). Guidance is also provided for defining and justifying specifications, selecting the appropriate tests to be run, etc. Q6A is a very comprehensive document that does not lend itself to a brief summary and should be directly referenced, when appropriate.

L. Q7A—Good Manufacturing Practices for Active Pharmaceutical Ingredients

This guidance provides detailed discussion and expectations covering the full scope of GMPs as they apply to the API, including the API prepared for use in clinical trials. As such, it is not practical to attempt to summarize its content in this work. The guidance is an excellent reference for use, when needed.

M. Q9—Quality Risk Management

The underlying principles for QbD development strategies are directly tied to appropriate risk assessment and risk management. Thus, Q9 provides essential guidance related to performing a true QbD program. The document outlines the general risk management process, including responsibilities, initiation of the process, risk assessment, risk control, risk communication, and risk review. Risk management methodology and tools are provided, along with consideration for integration of risk management into industry and regulatory operations. Annex II is a particularly valuable resource containing potential applications for risk management in a number of quality-related areas. Also, the glossary provided in Q9 is very useful to ensure that appropriate terminology is included in the QbD-based application.

N. Q10—Pharmaceutical Quality Systems (Draft)

Q10 when finalized will provide strong guidance to facilitate the operationalizing of risk management approaches within the company, looking over the full product life cycle. The document's stated goals are:

- Achieve product realization [i.e., to establish, implement, and maintain a set of processes that provide a product with the quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with marketing authorizations), and internal customers]

- Establish and maintain a state of control (i.e., to develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes. Quality risk management can be useful in establishing the monitoring and control system).
- Facilitate continuous improvement (i.e., to identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations, and pharmaceutical quality system enhancements.

Many relevant considerations are covered in this document, which will doubtlessly be a meaningful resource complementing Q8, Q9, and the eventual Q11 documents.

It is important to remember that the above ICH works are guidance documents, not regulations. As such, deviations are possible but should be limited and very well justified. Since these documents generally reflect the current agency thinking on the subject matter, it may be prudent to discuss any proposed deviation with appropriate agencies prior to submission of the marketing applications.

III. REGULATORY AGENCY GUIDELINES

While the evolution of the ICH has changed the focus of FDA, EU, and Japanese regulators from development of country-specific guidance documents to participation in the joint regulator/industry development of harmonized guidance documents, a number of important, country-/region-specific documents still exist to aid the CMC specialist. Many of these expand upon the works of the ICH, providing the current thinking of the respective agency on the information and data required to meet ICH standards. Additionally, the individual countries may issue documents that are considered valuable but are not yet chartered for work by the ICH. The primary discipline that has yet to be covered by the ICH are guidelines for postapproval submissions, which are clearly not harmonized among the three major ICH members at this time. Thus, a number of the individual guidance documents that have been recently issued focus on the postapproval arena. An overview of key API-relevant local guidance documents follows.

A. U.S. FDA Guidance for Industry Documents

A review of the recent FDA history related to API guidance documents, beyond ICH efforts, is very interesting, and clearly it is an ongoing story at this time. In the mid- to late 1990s, the FDA was actively working on meaningful guidance for the API content of new drug applications (NDAs) and principles to be used to assess and submit postapproval supplements related to API changes. Valuable guidances resulted, as did documents that received less favorable industry responses.

1. BACPAC

In the postapproval arena, the FDA looked to expand on its successful generation of Scale-Up and Postapproval Changes (SUPAC) documents by developing guidelines for "Bulk Active Postapproval Changes", or BACPAC. Initially, the goal was to issue a single BACPAC document covering the full scope of API manufacture and control. Journal articles and concept papers were published by industry groups, for example, PhRMA, in attempts to steer the FDA in its BACPAC efforts. After consideration of the industry recommendations and in an effort to provide guidance that would be appropriate to both innovator and generic manufacturers, the FDA decided to separate API manufacture to early and late stages. To achieve this separation, the FDA established the "final intermediate" as the point of differentiation between early- and late-stage processing. The final intermediate was defined as the last compound manufactured in the synthesis before the final chemical reaction to create the final API. The formation of salts, solvates, etc., was specifically excluded in the assignment of the final intermediate, which required the formation or breaking of a covalent bond in the structure of the molecule.

Utilizing this concept, the FDA issued a final guidance document, BACPAC I, in February 2001. BACPAC I covered changes to all process steps up to and including the formation of the final intermediate. Aside from major changes in the actual chemistry, few changes under BACPAC I required Prior Approval Supplements (PASs). This approach was very consistent with the evolving risk-based approach the FDA was developing, since typically early-step process changes had a significantly lower potential to impact the quality attributes of the final API compared with late-stage changes. The FDA also introduced the risk-based concept of assessing change at the closest point of the synthesis to the actual change. Assuming that good controls existed for intermediates produced during the synthesis, comparability of the pre- and postchange material could be demonstrated at the first intermediate following the recommended change or as appropriate at a subsequent intermediate or at the API itself. If comparability could be demonstrated prior to the final intermediate, the change could be immediately implemented and reported in the upcoming annual report (AR). If comparability was established at the final intermediate or API, the filing requirement became a Changes Being Effected (CBE). BACPAC I also clearly documented the criteria to determine comparability, with the focus on the resulting impurity profile of the material, and where appropriate the equivalence of physical properties. This risk-based approach was widely applauded by the industry and motivated some companies to actively develop meaningful quality controls on early process intermediates to take advantage of the BACPAC I guidance.

Following the issuance of BACPAC I, the industry anxiously awaited a similar BACPAC II document, covering changes post the final intermediate. When issuing BACPAC I, the FDA warned that BACPAC II would not provide comparable regulatory relief, since the risk for these late changes in the process to adversely impact quality was much greater. Industry groups attempted to steer the FDA toward using the concept of the "last true solution" as a point that could again separate risk assessments and hence filing requirements for post-approval changes under BACPAC II. It was generally accepted that changes following this last true solution had significant potential to impact quality and hence would require a PAS. Changes between the final intermediate and the last true solution would have varying potential for quality impact and hence could be considered for lesser filing requirements (AR or CBE/CBE-30). FDA efforts toward drafting BACPAC II were subsequently discontinued, and in 2006, the BACPAC I guidance was officially withdrawn. As of this time, no replacement postapproval guidance specific to APIs has been issued.

2. Postapproval Changes Guidance

Seeing the need for a comprehensive guidance for postapproval changes, the FDA drafted, issued, and later revised a document titled "Changes to an Approved NDA or ANDA." The document was intended to supplement the existing SUPAC guidelines. The initial formal release of this document in November 1999 met with mixed industry reaction. The guidance linked the filing category for a proposed change to the potential for adverse impact on the quality, purity, safety, or efficacy of the drug product. Changes with minimal potential impact could be submitted in the AR; moderate-impact changes required a CBE or CBE-30 filing, and those changes with significant impact required a PAS. The FDA categorized the changes into several areas, depending on the nature of change and its view of the impact potential, and added specific examples of those types of change. In each case, it had a generic statement for changes not described in the guidance, and these changes would require a CBE-30. In certain areas related to the API, there was a degree of ambiguity around the change types and their potential impacts. In addition, this guidance document did not specify the supporting data expected by the FDA to be included in the AR or supplement. On the basis of feedback, the FDA issued a "Questions and Answers" document capturing its thoughts on certain issues. The document was then formally updated in April 2004. Changes between the November 1999 and the April 2004 versions were not significant in the area of the API, and supporting data requirements were still omitted. This guidance remains in existence as of this date. Even though BACPAC I has been withdrawn, the FDA has stated that the principles put forward in that document can still, in conjunction with the April 2004 post-approval guidance, be used in assessing API process changes made prior to the final intermediate.

3. Drug Substance: Chemistry, Manufacturing, and Controls Draft

In 2004, the FDA issued in draft form a comprehensive guidance on preparation of the NDA section for APIs. This document contained the agency thinking on the contents of each CTD API section. The draft was very prescriptive by nature and raised numerous concerns from the industry. Significant comments were forwarded to the FDA during the public review of this document, and the document was subsequently formally withdrawn in 2006. One area covered in this draft that caused major industry concern involved designation of starting materials for the API process description. Certain aspects of the starting material draft will be discussed later in this chapter.

4. Other Existing API Guidance Documents

Copies of available FDA chemistry guidance documents are available at the link http://www.fda.gov/cder/guidance/index.htm#chemistry. The documents concerning APIs include:

- Changes to an Approved NDA or ANDA (4/2004)
- Changes to an Approved NDA or ANDA: Questions and Answers (1/2001)
- Comparability Protocols (2/2003, draft)
- Development of New Stereoisomeric Drugs (5/1992)
- Drug Master Files (9/1989)

- Drug Master Files for Antibiotic Drug Substances (11/1999)
- Format and Content of the CMC Section of an Annual Report (9/1994)
- INDs for Phase 2 and 3 Studies (5/2003)
- NDAs: Impurities in Drug Substances (2/2000; this document refers to ICH Q3A)
- Reviewer Guidance, Validation of Chromatographic Methods (11/1994; revised 5/2007 to include graphics)
- Submitting Samples and Analytical Data for Method Validation (2/1987)
- Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substance (2/1987)

The "Changes" documents were discussed earlier. Of the remaining documents on this list, the "Comparability Protocols" document warrants brief discussion. The FDA has established the comparability protocol as a potentially valuable tool to reduce the logistical impact from waiting for formal agency approval of PAS changes. Often, supporting data for a drug substance and/or a drug product made under a proposed change is required as part of the PAS submission so as to demonstrate comparability to prechange material or to ensure the purity, potency, safety, or efficacy of the postchange material. This postchange material would not be available for sale in the United States until the related PAS is formally approved—a time period of several months. The comparability protocol allows the sponsor to submit as a PAS information and evaluation criteria specific to the planned change prior to manufacture of material by that route. The FDA will review and, if appropriate, approve the comparability protocol. Data on change material, meeting the predetermined acceptance criteria, could then be submitted for FDA review as a CBE-30 once available, thereby reducing by several months the delay in marketing that material.

Very recently, the FDA has issued for comment a draft guidance on genotoxic impurities, which is actively generating public comments as this document is being authored.

B. EU/EMEA Guidelines

At this time, the European Medicines Authority (EMEA) has five active published guidance documents specifically related to the API, with a sixth in the review process:

- Active Substance Master File Procedure Rev 2 (4/2006 draft)
- Summary of Requirements for Actives Substances in the Quality Part of the Dossier (2/2005)
- Active Substance Master File Procedure Rev 1 (8/2004)
- Chemistry of New Substances (2/2004)
- Investigation of Chiral Active Substances (4/1994)
- Chemistry of Active Substance (10/1987)

In addition to the above, there are numerous active guidelines that impact the API, many of which refer directly to the ICH documents mentioned earlier. A complete list of current quality guidances can be found at the following link: http://www.emea.europa.eu/htms/human/humanguidelines/quality.htm. As a rule, these documents are reasonably consistent with corresponding FDA guidelines and hence will not be reviewed in detail.

The EU currently follows postapproval regulations that differ in nature from those described for the U.S. FDA. Until recently, the EU designated a relatively small number of potential changes for the API as Type I (minor) variations, with all other changes being considered Type II (major). The EU has recently further designated minor changes as either Type IA or Type IB, with some differences in the allowed implementation of the changes. At this time, these variation guidelines are under further revision, with the potential for inclusion of a filing comparable to the U.S. AR. Since the regulations are likely to change before this work is in circulation, it is suggested that the reader periodically monitor EMEA Web sites to locate the current requirements. A helpful link is http://www.emea.europa.eu/htms/human/raguidelines/post.htm.

Historically, EU guidance on key health-related issues, particularly impurity guidance, generally precedes efforts by the FDA or the ICH. A recent example is guidance related to genotoxic impurities, and another is the EMEA position on allowable residual levels of metals in the API. Thus, there are clear benefits for the CMC specialist to establish a practice of monitoring proposed and draft quality guidelines on a regular basis. Many U.S.-based companies do this through their local EU regulatory groups and/or through membership in the European industry groups such as EFPIA.

C. Japanese Guidance—The Revised Pharmaceutical Affairs Law

Until a few years ago, minimal information related to the API was required for registration of a medicinal product in Japan. Currently, however, the API section of the Japanese NDA is fairly consistent with that submitted in the United States and the EU. In fact, the Japanese agency requires that all parameters in the API synthetic route be designated as critical or noncritical in Module 1 of the CTD. These designations need to be data driven, and the agency has requested presentation of actual data supporting the criticality assessment.

Postapproval change regulations in Japan require a "Partial Change Amendment" for changes impacting critical parameters (this requires formal approval prior to implementation). Noncritical parameter changes can be submitted by a "Minor Change Notification" and may be implemented upon submission of the filing.

Undoubtedly, the above is a very limited and simplified discussion of the requirements in Japan, and further detail will need to be obtained through appropriate sources.

D. Other Country Guidelines and Requirements

Regulations and guidance documents related to APIs are under development or significant revision in several other countries worldwide. Canada, for example, is actively revising both its postapproval requirement guidelines and its Clinical Trial Application requirements. Both documents may be available by the end of 2009 and will represent the current thinking and expectations of Health Canada. A review of the draft postapproval document shows it to be very clear and comprehensive, making it a valuable resource for the CMC specialist for assessing filing and data requirements for changes in Canada.

Recent postapproval and marketing application submissions have resulted in questions and challenges from reviewing agencies that had historically been essentially silent on these issues in the past. Some of the requirements communicated by these agencies go beyond the expectations of the United States or the EU. This again points to the clear need for a strong regulatory surveillance practice within the company. Understanding the requirements and expectations for these markets will lead to more efficient and effective interactions during the review process and will help drive development activities to ensure that essential registration data are readily available.

IV. EVOLVING STRATEGIES AND ISSUES

A. Quality by Design

The biggest buzzword within the development areas of the pharmaceutical industry in the mid- to late 2000s is undoubtedly QbD. QbD is a development strategy that has evolved from the FDA-led risk-based filing efforts. It is a clear indication of the importance of this QbD approach that the latest ICH-Quality guidance documents, Q8 to Q11, deal directly with aspects of QbD. Innovator companies are designating significant resources to achieving internal QbD practices, capabilities and expertise, and most conferences and workshops dealing with pharmaceutical development are QbD based. With all the recent focus on QbD, it is interesting to hear the different definitions and interpretations of QbD that exist within companies and from company to company. To many, QbD is developing a comprehensive understanding of the manufacturing process in order to ensure that material meeting true patient needs is consistently produced. The key focus of QbD to some is the implementation of Process Analytic Technology (PAT) into the development and possibly the routine manufacture world. Clearly PAT is a valued tool for developing process understanding. Others suggest QbD is the result of meaningful risk assessment and risk management, leading to development of a well-understood process that will afford future regulatory flexibility. Some consider QbD the ability to utilize real-time release testing for their product, thereby eliminating or significantly reducing the need for formal laboratory quality assurance testing. Identifying and appropriately controlling the critical process parameters and critical quality attributes is part of QbD, as is establishing appropriate, data-driven design spaces based on multivariate development experiments. A comprehensive, holistic control strategy is unquestionably a key element of QbD. Clearly, all of the above are relevant aspects of QbD.

QbD gained significant momentum from the FDA-initiated "Pilot Program," where companies voluntarily submitted QbD-based filings for actual NDA product applications and worked closely with the FDA prior to submission and especially during the review and approval process. The companies then had the opportunity to retrospectively review the registration process for products using QbD with the FDA. An interesting outcome of the pilot program was comments by the FDA that the companies involved in the exercise took very different approaches to the QbD-driven development and filing. Experiences from the program have helped further shape agency expectations and industry practices for QbD, leading to more meaningful risk assessments, improved multivariate experimental design and data interpretation, and better-defined, more holistic control strategies.

At this time, QbD continues to be an evolving process, particularly outside the United States. Regulatory agencies are establishing their expectations for QbD submissions, and the industry is adapting its practices on the basis of its increasing knowledge and experience in this area. Companies are recognizing the need for better knowledge management systems to handle the increased amount of information and data being generated during development. The FDA is still an active leader in the world of QbD and is working on guidance for establishment of a Postapproval Management Plan (initially referred to as a Regulatory Agreement) reflecting the process knowledge and control strategy contained in the application. Many believe a key payback for the additional efforts to develop a product using QbD would be added regulatory flexibility to make future changes with no or lesser filing requirements.

QbD will clearly be an essential element of pharmaceutical development for the foreseeable future, and the CMC specialist would benefit from a working knowledge on this subject. The best way to gain that understanding is to become very familiar with the aforementioned ICH Q8 to Q11 (when issued) documents and to review documents like the mock development filing documents. These mock documents are being prepared to increase QbD awareness and establish and share best practices without giving proprietary product information and have been actively discussed by joint regulator/industry working groups. Many gain knowledge about QbD by listening to presentations by key regulatory authorities or by participating in internal or industry working groups on the topic.

It will be very interesting to monitor the evolution of QbD in API development, especially in light of the movement to outsource more and more of API manufacture. Some believe outsourcing and continuous improvement are mutually exclusive initiatives. Once outsourced, the supplier is expected to produce the material using the established process, meeting the defined specifications, with minimal changes to the process or testing requirements. Transfer of the knowledge gained by the innovator during development to the contract facility would require additional resources, without an obvious benefit. On the other side of the argument, QbD development could result in the outsourcing of a better-optimized, cost-efficient process with meaningful real-time controls for critical attributes. This should lead to a more robust process, fewer atypical events and deviations, and a lower quality rejection rate, all of which would translate into direct cost benefits.

B. Starting Material Requirements

After QbD, one of the most discussed topics in the industry today is the definition of the regulatory starting materials for a given process. The API starting material is defined in ICH Q7A as:

> A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure.

By definition, introduction of the starting material into the process is the point at which GMPs apply. Thus, manufacture of the starting material is not bound by GMP regulations. Additionally, from a regulatory standpoint, the process description in the marketing application is documented from the introduction of the starting material. Changes to the route of manufacture of the starting material would not be contained in the registration document and hence would not be subject to postapproval filing requirements. For both reasons, it benefits the industry to define the starting materials as far into the process as possible. While there are indirect benefits to the regulators from this approach, most notably a reduced workload in assessment of early-step manufacturing process changes, there is also a potential increased risk associated with this practice. The main concern would be the introduction of new impurities as a result of changes in the manufacture of the advanced starting material. The existing analytical methods may or may not be specific toward the new impurity. In addition, since there are no GMP requirements, the regulatory agencies have no trigger to inspect the starting material suppliers to ensure they are using at least minimally acceptable operating practices.

Given that the ICH definition is very broad and can be used to argue both industry and regulator expectations, this is clearly an area in need of a compromise position based on sound science and meaningful risk assessment. In its 2004 draft API guidance, the FDA attempted to define starting material qualification criteria. Starting materials could always be commercially available items but also can be specifically manufactured by an external supplier or internally by the company, provided that they were "several" steps removed from the final intermediate and had controlled impurity profiles, including a tight limit on newly observed impurities. On the whole, the FDA guidance was viewed as very restrictive to the industry, which prefers to stress the ability to adequately control the material and to understand the fate of impurities in the downstream process. The idea of "propinquity" (i.e., the number of steps prior to the final intermediate) was not considered the driving factor for starting material definition. It should be noted that the FDA withdrew this draft guidance in 2006.

The gap between regulator and industry thinking on this topic remains today. There have been a number of publications or concept papers on the subject, but to date no guidance document on the topic has been finalized. There is a proposal to address starting materials in the development of ICH Q11, but it remains to be seen whether this will occur.

Absent of definitive guidance, companies are using very different practices for defining starting materials. Some will routinely discuss starting material designation with the agency prior to submission of the marketing application. Others take very conservative approaches consistent with the "propinquity" standards from the draft FDA guidance. Still others will take an aggressive approach in defining starting materials in the application and attempt to defend their selection in the document or during review.

This will be another very interesting topic to monitor in the coming years.

C. Genotoxic Impurities

Much attention is now focused during agency review on impurities with genotoxic potential; that is, those that have a high potential to be carcinogenic in humans. There is no argument that it is important to appropriately control these impurities in the API as well as the drug product. The issue at this time is the steps that need to be taken to evaluate the process for materials with genotoxic potential and the levels that should be established for control of such materials. Several viable approaches are being used by the industry, including direct testing of API or intermediates and/or using screening processes to identify materials with genotoxic potential on the basis of their structure. Both the FDA and the EU have published draft guidances on this topic, which, when finalized, will hopefully provide better clarity on the regulatory expectations for genotoxic impurity control.

D. Complexity of Outsourcing

As previously mentioned, there is a strong initiative within the industry to outsource manufacture of late-stage intermediates and finished APIs to lower-cost suppliers. From a regulatory prospective, this practice increases the complexity of the registration documents and potentially the workload for the industry and regulators alike. While responsibility for the quality of the outsourced API resides firmly with the sponsor of the marketing application, the agency is still charged with ensuring the safety of the patient population in its country. Thus, it needs to not only be satisfied with the quality and controls in place for the material as described in the marketing application [or a drug master file (DMF) referenced in the application], it must also be satisfied that the sponsor has in place the appropriate controls and quality systems to monitor the ongoing suitability of that material. Even though the supplier must utilize an approved GMP facility, this may lead to a more in-depth review by the agency of the sponsor's change control procedures, the supplier inspection practices, etc.

V. THE FUTURE

Given the pressures on both the industry and the regulators due to resource limitations and the desire to reduce costs, it is becoming increasingly more critical that clear, meaningful guidelines are established in the pharmaceutical industry. It is hopefully evident from the discussions in these two regulatory chapters that industry practices and regulations governing the API are continuing to evolve and progress. At this time, the regulatory requirements still differ from country to country, and these differences have and continue to place a significant burden on the industry. The ICH has taken an important step in developing and publishing meaningful guidance documents for the industry, and the positive impact of its activities is referenced throughout this work. There remain cases where individual agencies will enforce requirements beyond those contained in the ICH guidelines; however, the guidelines are now often cited and accepted in a majority of regulatory filings and are utilized in development of new medicinal products, including those developed using QbD principles. The ICH initiative has clearly shown the synergies that can be achieved when the industry and regulators work together toward common objectives. We look forward to increased levels of industry-regulator cooperation in this area in the years to come as we move further into a global, risk-based environment focusing on the development of safe, effective medicines to meet critical needs.

7

Validation of Active Pharmaceutical Ingredients

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I. HISTORY

Validation was initially introduced in the 1970s to the pharmaceutical industry as a means of more firmly establishing the sterility of drug products where normal analytical methods are wholly inadequate for that purpose. In following years, its application was extended to numerous other aspects of pharmaceutical operations: water systems, environmental control, tablet and capsule formulations, analytical methods, and computerized systems. Individuals working with bulk pharmaceutical chemicals (BPCs) were particularly reluctant to embrace validation as a necessary practice in their operations. Industry apologists explained this lack of enthusiasm in terms of differences in facilities, equipment, technology, hygienic requirements, cleaning methodologies, operational practice, and numerous other aspects of disparity that seemingly justified the recalcitrance of this segment of the industry. This view was widespread in the bulk chemical industry through the end of the 1980s.

The extension of the concepts that have made validation such an integral part of practices across the health care industry to the production of BPCs seems obvious in retrospect. Yet, for many years, there existed a general reluctance to introduce validation into BPC activities. While there were some modest efforts, it was not until some time after the biotechnology industry became technically and commercially viable that any significant effort was initiated. The production of biotech products for registration in the United States requires the approval of the Food and Drug Administration's (FDA) Center for Biological Evaluation and Research (CBER). The CBER required extensive validation of fermentation, isolation, and purification processes utilized in the preparation of biologicals (1). An objective comparison of BPC operations relative to those performed in the early stages of biologicals would reveal minimal differences. The production methodologies for many classical BPCs, for example, penicillins, cephalosporins, and tetracyclines, are nearly indistinguishable from those utilized to prepare tissue plasminogen activator (tPA), erythropoietin (EPO), and other biologicals. With this realization, the advent of validation for BPCs was apparent to all and was increasingly imposed on the industry.

In 1990, the United States Pharmaceutical Manufacturers Association (now called PhRMA) formed a committee to define BPC validation concepts (2). This committee's efforts culminated in 1995 when it issued its finished draft. This document served as a guide to the authors in the development of this chapter. Of necessity, considerable clarification and expansion of the material contained has been necessary to complete this effort.

In the late 1990s, a new term started to appear, first in Europe, but soon it spread across the entire industry—"active pharmaceutical ingredients," or APIs.

Those who first used the new term suggested that it was synonymous with BPCs. Since that time it has become increasingly common in the industry to speak only of APIs. A part of the rationale for this initiative has been voiced as a move toward harmonization. In publications since that time, "API" has largely supplanted "BPC" as the descriptive term for these products. It will be used throughout the remainder of this chapter.

The official requirement for validation of API processes was formally established in *Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (3). This harmonized guidance document was the result of a multiyear effort by the International Conference on Harmonization (ICH). This guidance document addresses the subject of validation briefly and employs the same definition the FDA has adopted for other processes (see the section "Definition of Validation"). This chapter provides recommendations for validation consistent with the Q7A guidance.

In late 2008, the FDA published a revised guideline on process validation and explicitly included APIs as falling under the guidance (4). This should foster greater consistency of the validation approach between dosage form and API manufacturing in the coming years.

II. DEFINITION OF VALIDATION

There are innumerable definitions of validation that have been written over the nearly 30 years since its appearance in the pharmaceutical industry. Rather than foster new definitions with the context of this chapter, the authors have chosen to draw on some of the more widely quoted definitions. The FDA had long defined process validation as follows: "Process validation is establishing documented evidences which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics" (5). This definition is referred to in the FDA's subsequent guidance specific for APIs (6). The more recent FDA guideline, however, defines validation as follows: "Process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products." This is more aligned with the authors' long-standing view of validation as a "life cycle" concept.

III. REGULATIONS

Regulations specific to control APIs are a relatively new concept; for many years the FDA's policy was to apply a limited enforcement of the subpart 211 regulations for finished pharmaceuticals (7). In recent years, the FDA has endeavored to harmonize its approach to API regulation with the rest of the world and has issued a guidance document that draws heavily on subpart 211 (8). This effort followed the issuance of a *Pharmaceutical Inspection Convention* document that addressed the same subject in a different format (9).

IV. APPLICATION OF VALIDATION

Some discussion of validation approaches utilized for APIs is essential for following this chapter. The approaches for APIs are essentially the same as those utilized for other processes and systems. This discussion serves to highlight the nuances of validation as they apply to APIs.

V. LIFE CYCLE MODEL

Contemporary approaches to the validation of virtually any type of process or system utilize the "life cycle" concept (10). The use of the life cycle concept was embraced by the FDA in its 2008 draft guidance on process validation, reaffirming the appropriateness of this approach that had been adopted previously by numerous practitioners. The life cycle concept entails consideration of process or system design, development, operation, and maintenance at the onset. Use of the life cycle concept helps to provide a system that meets regulatory requirements but is also rapidly placed into service, operates reliably, and is easily maintained. While the life cycle concept is best suited to new products, processes, or systems, it certainly has applicability for existing systems as well. Existing systems that have never been previously validated can be reviewed against the same validation criteria that would be imposed for new systems. While these systems are likely to be deficient with regard to current requirements, the life cycle model provides a means of upgrading their programs to be on a par with newly developed systems. This is especially important for BPCs, given that the validation of these processes has lagged behind many of the other areas of the industry where validation has already been instituted. It is perhaps safe to say that the first validation efforts to be utilized for APIs will likely be retrospective ones, following the existing system path to enter the life cycle model.

VI. VALIDATION OF NEW PRODUCTS

The validation of a new API entails practices that parallel those utilized for the introduction of a new pharmaceutical formulation. Thus a large part of the initial validation effort must be linked to the developmental activities that precede a commercial-scale operation. The similarity is such that aspects of reaction and purification methodologies should be as similar as possible, given of course the difference in the scale of the equipment utilized in the commercial facilities. Any differences between the API processes utilized for the formulation batches used to establish clinical efficacy and the commercial material and their impact on the API—chemistry, purity profile, stability, crystal morphology, and other key attributes—must be closely evaluated. The developmental laboratory has the responsibility for determining optimal reaction conditions, including time, temperatures, raw material purity, molar ratios, solvent selection, crystallization method, wash volume, drying conditions, etc. Of primary concern is the identification of critical control parameters, that is to say, those that impact quality, purity, safety, and efficacy. The concerns to be addressed in any individual API validation program are of course unique to that process; the inclusion or exclusion of any single factor as a consideration in API validation is an arbitrary one determined by the authors. Chemical reactions are among the more complex processes to be subjected to validation, and the number of critical factors in even a single reaction can be quite extensive. The amount of information that must be generated during development to support a validated API process is correspondingly extensive. The necessary information can be assembled into a technology transfer document that conveys the collected experience gained during development to those responsible for the commercial production of the API. The success of a developmental organization is better assessed by the quality of the information it conveys to document its efforts than by the sophistication of the chemistry utilized to make the API. The technology transfer document is likely to be of central interest to FDA inspectors during the conduct of a preapproval inspection of the facility prior to approval (11).

VII. VALIDATION OF EXISTING PRODUCTS

Validation of BPCs is a still relatively new concept for the industry to address. As such many API products have been introduced to the market without any significant validation in place. As a consequence, the first efforts to validate these products will undoubtedly employ retrospective methods. The trending of results derived from in-process and release testing of these products and processes will serve as the basis for these efforts. Given the FDA's general dissatisfaction with retrospective approaches, it is doubtful that these early efforts will remain the only approaches utilized. The use of either prospective (in which three batches must be produced before the process can be considered validated and any of material released for sale) or concurrent (in which individual batches are released while continuing to accumulate data toward a three-batch validation) approaches are certainly acceptable; a decision to use those approaches while raising less regulatory concerns will also require a longer time to execute and a larger resource commitment. The establishment of priorities for validation of a large number of API processes generally follows economic concerns, with those products that provide the largest contribution to the firm's profitability being the initial focus of activity. Regardless of how the first validation efforts were completed, the adoption of the life cycle model for maintaining products in a validated state is becoming increasingly widespread.

VIII. IMPLEMENTATION

The validation of any process or product relies on several supportive activities. Validation in the absence of these activities has only minimal utility, as it is only through the integration of these other practices that meaningful validation can be accomplished. Several of these activities are defined in current good manufacturing practice (cGMP) regulations, while others are an integral part of a company's organizational structure or are closely associated with validation itself (12).

A. Equipment Calibration

Calibration is the process of confirming the accuracy and precision of all measurements, instruments, etc., to ensure that the measured variable is being accurately monitored. Calibration includes demonstration of conformance to applicable national standards such as National Institute of Standards and Technology (NIST), Deutsches Institut für Normung e.V. (DIN), or British Standard (BS) for all key parameters. This is a universal cGMP requirement across the globe.

B. Commissioning

Maturation of facility qualification concepts and an awareness that a hierarchy exists for the systems installed in the facility has increasingly led to the adoption of an approach to system/facility start-up, termed "commissioning." Commissioning is a good engineering practice in which systems are confirmed as acceptable for use. All systems need commissioning in order to ensure their fitness for purpose and compliance with detailed engineering and vendor specifications. Also, commissioning affords technical experts the opportunity to inspect, start up, correct, and adjust systems without resorting to the more formal and rigorous expectations associated with equipment qualification (see the section "Equipment Qualification") (13). Systems and equipment within the facility can be reviewed from a risk-based perspective, and those without significant risk to product quality may then be placed into use without further testing or review. This would be appropriate for such systems as heating and cooling sources (e.g., steam, cooling water), nonproduct contact gasses (e.g., instrument air), and heating, ventilating, and air-conditioning (HVAC) systems serving closed processes (e.g., reactor halls).

C. Equipment Qualification

Where equipment or systems are assessed to have a significant risk related to product quality, most firms require additional oversight, including that of the quality unit. Equipment qualification is a precursor to process validation and focuses on physical and functional aspects of equipment that are determined to affect product quality, in this case the quality of the API. Equipment qualification expectations should be linked to user requirements specifications (URS), which are in turn derived from critical process requirements (14). For example, if a synthesis reaction occurred best at pH 1, it would mandate that glass or Hastelloy be utilized, which would then become a qualification expectation for materials of construction on the vessel and process piping. As API facilities are commonly utilized for more than one reaction over the course of their operational life, flexibility should be the goal in performing equipment qualification. The equipment should be evaluated across the full breadth of its performance capabilities, and future uses may require conditions quite different from those needed initially.

There is *no* requirement for a formal separation of the activity into distinct elements, such as installation and operational qualification. It has become increasingly common in recent years to combine these activities under a single effort. For the sake of those who still separate the activities, individual descriptions have been provided.

1. Installation Qualification

Installation qualification is documentation that the equipment was manufactured and installed in accordance with the intended design. This is essentially an audit of the installation against the critical equipment requirements affecting quality of the API.

2. Operational Qualification

Confirmation that the equipment performs as intended entails evaluation of performance capabilities. It incorporates measurements of speeds, pressures, and other critical process parameters.

D. Process Development

The development of products and processes, as well as the modification of existing processes, should be conducted to provide documented evidence of the suitability of all critical process parameters and operating ranges. This effort serves as a baseline for all product validation activities. The integration of development into commercial-scale operations became a requirement with the advent of the FDA's preapproval inspection program (11). The importance of well-documented developmental activities to support subsequent commercial-scale production is essential in the validation of API. It is customary for many unit operations (reactions, separations, catalyst reuse, solvent reuse, etc.) to be initially confirmed on a laboratory or pilot scale prior to their eventual validation on a commercial process scale.

E. Process Documentation

Process documentation is an often overlooked activity, wherein the results of the development effort are delineated in sufficient detail in process documentation so that the variations in the process as a result of inadequately defined procedures are eliminated. While master batch records have long been a cGMP requirement, their adequacy is essential to the maintenance of a validated state.

F. Performance Qualification (Testing)

Performance qualification is that portion of the overall validation program that deals specifically with the evaluation (validation) of the process. It includes protocol development, data acquisition, report preparation, and requisite approvals. In the distant past this activity was considered "process validation," but over the years the industry has come to realize that validation encompasses a broader spectrum of activities and the continued use of the word "process" is limiting.

G. Change Control

Change control is a cGMP requirement that mandates the formal evaluation of the consequences of change to products, processes, or equipment. At least two distinct types of change control exist because of the different disciplines that are central to the evaluation of each (15).

1. Process Change Control

Process change control is a system whereby changes to the process are carefully planned, implemented, evaluated, and documented to ensure that product quality can be maintained during the change process. This type of change control is the province of the developmental scientist and production personnel.

2. Equipment Change Control

Equipment change control is a mechanism to monitor change to previously qualified and/or validated equipment to ensure that planned or unplanned repairs and modifications have no adverse impact on the equipment's ability to execute its intended task. This procedure usually entails close coordination with the maintenance and engineering departments.

IX. BULK PHARMACEUTICAL CHEMICAL VALIDATION

The focus of this chapter is BPC validation. To this point, aside from the history section, the information presented would apply to almost any type of process validation. That commonality with other older validation efforts is deliberate.

API validation is unique only to the extent that APIs are unique. The underlying maxims of success for validation (the knowledge and understanding of the scientific basis on which the equipment or process is based) are universal. Mastery of the overall approach equips one to effectively employ those concepts in a variety of settings. Some knowledge of the key concerns in the production of APIs is essential to understanding how the validation of their preparation should be carried out.

Life cycle validation concepts apply to all stages of API manufacture. This means that each step from the introduction of a starting material should be well characterized and understood on the basis of developmental data and production experience. ICH Q7A defines starting material as follows: "An API starting material is a raw material, intermediate or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API" (16). Steps prior to the starting step often take place outside of the API manufacturing site and are not considered in this discussion.

Although validation concepts of process understanding and control apply, many firms do not require formal validation documentation until some later process stage that is determined to have a direct effect on the quality of the final API. One approach suggested in the FDA's API guideline is to begin formal validation documentation at the so-called API step, the step where the molecule contains the chemical moiety determined to embody the pharmacological activity of the API.

In any case, regardless of when and where formalized documentation is required, the principles of this chapter apply across all API manufacturing steps. Adequate documentation should be provided to ensure a continuing understanding and control of even the early steps of the process.

A. Unit Operations

APIs are the result of a series of chemical reactions in which materials, called reactants, are brought together under appropriate conditions whereby the reaction takes place and the reaction product is formed. Under even the most ideal circumstances, the desired product must be separated from unreacted raw materials, by-products, solvents, and processing aids before it can be utilized in further processing. In the analysis of these processes, chemical engineers have found it convenient to divide the overall process into a series of unit operations (some of which are physical in nature, while others are chemical in nature). The unit operations approach is beneficial because a complex many-step process can be separated and better understood as a series of simpler activities (unit operations) that are more easily interpreted.

Among the more common unit operations are mixing, heating, drying, absorption, distillation, condensation, extraction, precipitation, crystallization, filtration, and dissolution. There are other less common unit operations, but the more important aspect is the subdivision of a lengthy process into smaller and more readily understood segments. The benefits to be gained from this approach are obvious; once the underlying principles are understood for a specific unit operation, those concepts can be reapplied in other steps or processes where that same unit operation is employed. In the validation of API processes, the ability to use standardized methods for each unit operation can make what would otherwise be an impossible task into a manageable one. The unit operation approach is of such utility that it has been applied in pharmaceutical dosage form manufacturing as well, where the same basic procedures are often encountered, that is, mixing, milling, filtration, etc.

B. Physical Parameters

A concern that has been sometimes neglected in the preparation of APIs relates to the control of physical parameters of the end-product material. Often the focus of API development and processing is on chemical purity and yield, as those aspects tend to have the greatest economic significance. There is relative indifference to physical parameters such as size, shape, and density compared with the seemingly more important concerns such as potency, impurity levels, and process yield. The authors have observed numerous situations where this inattention has resulted in processing problems at the dosage form manufacturing stage. In each instance, it was often the case that the physical parameters of the end product had been virtually ignored in deference to concerns over chemical purity (17). The FDA's preapproval inspection initiative indicated an awareness that these concerns have come to their attention during the course of New Drug Application (NDA) reviews and inspections (11).

The most extreme circumstances where physical parameters are of critical importance are for those materials where different crystalline forms are possible. The different polymorphs may have decidedly different characteristics with regard to crystal shape, size, and, most important, solution characteristics. Many important pharmaceutical chemicals exist in more than one crystalline form, and the manufacturer must ensure that only the desired form is being produced. One of the major concerns voiced by regulators is the potential hazard in using brokered active ingredients (6). The ability to match the purity profile of an API is not sufficient if the crystallization is from a different solvent system or at different conditions. An entirely different material may result, with profoundly different pharmacological properties. The absence of detailed information on the isolation process used may cause difficulties should the real source of the material (the broker's supplier) change.

C. Chemical Purity

Central to the preparation of APIs are issues relative to the purity of the desired material. Until recently the only concern was whether the material met the minimum potency requirements. A typical requirement would be a minimum potency specification of 98%. Any lot that had an assay higher than 98% would be acceptable. Awareness that the small amount of material that is not the desired molecule could cause adverse reactions led to the establishment of purity profiles for APIs. Using a purity profile approach mandates that the firm identify the impurities present. Current FDA expectations are that firms should characterize all impurities that constitute more than 0.1% of the final API and perform toxicity testing on any impurity that is at a concentration higher than 0.5% (6). The establishment of a purity profile for a molecular entity ensures that process changes that might result in a change in the by-products and other materials isolated with the desired material do not impact the safety and efficacy of the final product.

D. Analytical Methods

As with other types of product validation activities, API validation cannot proceed without validated analytical methods. The most significant difference in the validation of APIs is the number of analytical methods that must be addressed. Analytical methods are needed for each stage intermediate, identifying and quantifying the major by-products at each stage, as well as the desired chemical moiety. Clearly the scope of the analytical method validation for APIs represents a larger effort than is normally associated with process validation activities. A comprehensive review of analytical method validation can be found elsewhere in this volume.

E. Facilities

API facilities are vastly different from most other types of facilities in the pharmaceutical industry. The equipment is designed for specialized procedures and as such bears little resemblance to those that might be found in a dosage form facility. Most API equipment requires a broader range of utilities and a seeming maze of piping to perform properly. Chemical reactions are sometimes performed at temperatures in excess of 120°C or less than 0°C and require specialized heat transfer fluids to maintain those temperatures. Many reactions utilize solvents as reaction substrates or in the isolation of the materials. These solvents may be introduced via piping systems that supply the various pieces of equipment. Distribution systems for compressed gases either used in the reaction or used to make the equipment inert are also common. In many older API facilities, it is common to see multiple vessels at different elevations arranged around an open bay. In these facilities, several different chemical reactions might be underway in different vessels for different products at the same time. In a dosage form facility this type of arrangement would be viewed with some skepticism. In API production, the reactions and unit operations take place within closed equipment, minimizing the potential for cross-contamination. The difference between API and dosage form facilities is most evident in warmer climates. In these areas, the API facility may be little more than structural support for the equipment and staging areas for material, with no surrounding building. In effect the equipment is outside, fully exposed to the environment. For certain API processes such as solvent recovery and hydrogenation vessels, the equipment is located outside in even northern climates, because of either sheer size or safety concerns. These types of arrangements are not typical for the later steps in the synthesis. Isolation of the completed API is usually performed in rooms specifically designed for that purpose and entails some level of environmental control to help ensure the purity of the API if it will be exposed. True clean rooms [i.e., rooms meeting the requirements of an international standard such as International Organization for Standardization (ISO)] are rarely employed.

F. Pure Rooms

In the preparation of APIs, it is common for the last step in the process to be completed in an environment far different from that in which the rest of the synthesis is performed. The term "pure room" is used loosely—there are no regulatory requirements for these rooms, and the actual terminology varies considerably from firm to firm. Even without regulatory impetus, some firms have gone so far as to classify their pure rooms at Class 100,000 (ISO 7) or better

(18,19). After the crystallization of the API, it is important to protect the product from airborne particulates and other foreign matter that might end up in the finished material. For this reason it is common in many companies to perform a filtration of the active material while still in solution. The filtration removes particulates that may have accumulated in the material up to that point. After the filtration, the solution is introduced into the crystallizer in the pure room. The room itself is designed to minimize the opportunity for introduction of contaminants into the bulk material and may or may not be a classified environment. The crystallizer is often subjected to extraordinary cleaning before the start of the process so as to ensure its suitability for the final bulk isolation. Following the crystallization, the API is centrifuged, washed, dried, milled, and packaged in the pure room. It should be noted that API processes that use pure rooms are not intended to be sterile; the production of sterile APIs requires a much higher level of control over the environment, equipment, and methodologies and is described elsewhere in this text.

G. Qualification of Equipment

The qualification of API process equipment, including reaction vessels, receivers, crystallizers, centrifuges, dryers, filters, distillation columns, solvent distribution systems, etc., is a well-defined activity. While this equipment is somewhat different in design and operating features than the dosage form equipment that has been the subject of the majority of papers on the subject, the same general principles apply. Reaction vessels, receivers, and crystallizers differ only minimally from formulation and water-for-injection (WFI) tanks. Some API dryers are identical to those utilized in tablet departments. Solvent distribution systems are piping systems and may resemble WFI distribution systems. Some pieces of equipment such as distillation columns and continuous reactors may not have counterparts in the dosage form side, but an understanding of the objectives of the equipment qualification should make the development of suitable protocols straightforward.

H. Configuration Confirmation

In multipurpose API facilities, the fixed equipment installed may be configured differently for different reactions. In these facilities, campaigns of one reaction may be followed by a reaction for a different product after a change in configuration. Putting aside cleaning considerations for a later portion of the chapter, verification of the systems configuration should be performed. In effect, the reaction train must be requalified at the start of each campaign to ensure that the proper arrangement of valves, transfer lines, instruments, and other items is established for the process to be introduced. Some firms run a water or solvent batch, which simulates the process to verify that the proper connections are in place and that there are no leaks in the system. Following this trial batch, the system is then readied for use with the solvents that will be utilized in the process.

I. Environmental Control

The usual concerns relative to the environment in which the production activities are performed are not as significant in API manufacturing as they are in the preparation of pharmaceutical dosage forms. The introduction of microbial or particulate contaminants at early stages of the process is unlikely to be of significance. API reactions utilize high temperatures, extremes of pH, and aggressive solvents that can minimize the impact of any microbial contamination. Filtration is a frequent part of API processing in the form of carbon treatments and other unit operations whose intent is to remove unwanted by-products, reactants, and solvents. In the course of these measures, incidental particulate contamination is also removed. The use of pure rooms as outlined earlier serves to minimize contamination at the last step.

J. Worker Safety

The safety of the personnel who work in the facility is always a major concern. Exposure to toxic substances is greatest when the operator is adding materials to or removing materials from the equipment. The use of air extraction equipment, isolation technology, automated handling, and other means of minimizing human contact with toxic materials is nearly universal. The assessment of worker safety should also embrace exposure to vapor phase hazards, and leak testing of process trains should be performed where hazardous gases are present. Validation of the effectiveness of this equipment is not mandatory from a cGMP perspective but is certainly beneficial.

K. Process Water

The water used in API production is usually deionized water through the early process stages. If the product is isolated from a water solution in its last step, then a compendial grade of water, purified water, or WFI may be utilized, depending on subsequent steps in dosage manufacture and the final use of the product. Cleaning of equipment can be performed with city water, provided the last rinse of the equipment is with the same water utilized in the process step. The validation of water systems has been well documented in the literature (20,21).

L. Process Gases

Some API reactions utilize gases as reactants or are performed under a gas blanket. The gas delivery system may start at either a large high-pressure bulk storage tank or a bank of gas cylinders. Attention should be paid during the installation of the system to ensure that the materials of construction utilized in the system are compatible with the gas being handled. Distribution systems for these gases require qualification, but their similarity to gas distribution systems used in dosage form facilities means that the basic approach is well defined in the literature. For safety considerations particular attention should to be paid to proper identification of process gas lines throughout the facility (see the section "Compressed Air").

M. Compressed Air

Air that is classified as breathable should receive an intensive qualification effort, especially with regard to the verification of "as built" drawings, confirmation of proper identification, as well as any safety- and purity-related issues. The emphasis given to breathable air is due to the number of unnecessary deaths that have occurred in the industry as a consequence of misidentified gas lines. Where air is utilized as a reactant in an API operation, it should be treated as described previously under process gases. Instrument air requires the least intensive effort, as the adequacy of the installation can be often confirmed indirectly during the calibration and qualification of the process instrumentation. A single compressed-air system could serve as the source for more than one of these air systems simultaneously. In this instance the advice provided for the most critical application is appropriate throughout.

N. Jacket Services

It is common in API facilities, especially those that are reconfigured frequently to accommodate the production of different materials, to have each major vessel equipped with identical utilities such as chilled water, plant steam, and compressed air. The use of identical utility configurations on the vessels maximizes the flexibility of the facility, reduces the potential for operator error, and simplifies the design of the facility. The control systems for these jacket services on the vessels would also be identical. Under these circumstances the qualification effort is greatly simplified through the use of identical requirements.

O. Solvent Distribution

Many facilities use one or more solvents repetitively. In these instances, the installation of a dedicated distribution system for the solvent to the various use points can be justifiable. These systems may be lengthy lines from the bulk storage area (tank farm) to the various locations in the facility where the solvent is required. In some cases, a chilled solvent system may be present to provide chilled washes for use in centrifugation. Depending on the solvent, specialized piping or gasket materials may be necessary to avoid leaks or corrosion of the system. Qualification of these distribution systems is easily accomplished.

P. Solvent Recovery and Reuse

The reuse of organic solvents in an API system is widespread, especially given the increased cost of these materials and the environmental difficulties associated with their proper disposal. This reuse is achieved through defined procedures for the recovery of the solvents from distillates, extractions, and spent mother liquors. Where recovered solvents are utilized in the production of an API, the validation of the recovery process is strongly recommended. The validation of the recovery process would include all steps in the process and confirm the acceptability of the recovered solvent in the processes it will be utilized in. The validation of the use of recovered solvents could be part of the development of the process. Repeated recycling of solvents could result in the concentration of trace impurities that could adversely affect reaction chemistry. At the very least, recovered solvents should be subjected to release testing and shown to be comparable to fresh solvents. The complexities associated with the validation and reuse of recovered solvents should not be overlooked.

Q. Multiple Crops

In the crystallization of some APIs, multiple crops are sometimes utilized to maximize the amount of material isolated. Even where the cost of the materials being isolated is not high, the ability to increase the overall yield through the collection of multiple crops is frequently a routine part of the process. A related technique is to recycle the mother liquors without additional treatment from the crystallization to the beginning of the process. Whether through multiple crops or recycling of the mother liquors, both of these processes result in the concentration and/or retention of impurities. The validation of these practices must be part of the development effort for the process and reconfirmed on the commercial scale.

R. Catalyst Reuse

Precious and semiprecious metals and other materials are often utilized as catalysts in the conduct of certain chemical reactions, for example, hydrogenation. While the quantity of catalyst required in any particular reaction is quite low, the cost of these metals is such that recovery is mandated. As the amount of catalyst required to support the reaction is generally supplied in excess, it is frequently possible to return the catalyst to the start of the process step without loss in effective yield. The reuse of the catalyst in this manner must be supported by appropriate development work.

S. Waste Treatment

The nature of the materials, by-products, and solvents utilized in the preparation of APIs ultimately results in any number of waste treatment problems. The validation of these treatments is certainly *not* a cGMP-required activity. Nevertheless, consideration should be given to those activities to ensure their reliability. Such efforts can aid in attaining environmental approval for the facility.

X. IN-PROCESS CONTROLS

BPCs resemble other types of products validated in the pharmaceutical industry in that they utilize various in-process controls to support and monitor the process through its execution. Typical controls that might be part of an API process include material specifications.

A. Material Specifications

The controls of reactants, solvents, intermediates, and finished materials employ formal specifications for key parameters. The importance of these controls increases toward the end of the synthesis, and any of the controls that follow the API step are certainly important enough for the efficacy of limits set for these controls to be a major part of the developmental process. Foremost among the considerations in the latter process steps should be the impurity profile of the key intermediates (see the section "Purity Profiles"). Physical parameters (size, shape, crystalline form, bulk density, static charge, etc.) of the finished API are sometimes considered less important them chemical purity. When the API is formulated in a solid or semisolid dosage form, these physical parameters may assume far greater significance.

B. Purity Profiles

Within the specification parameters, prominence is often given to the establishment of purity profiles for the key intermediates and finished goods. The FDA mandates the identification of all impurities with a concentration greater than 0.1% and generation of safety and other critical information for impurities at levels of 0.5% or higher (6). The establishment of purity profiles for the final APIs provides for confirmation of the safety of the active material. It is often beneficial to establish purity profiles for intermediates earlier in the synthesis to prevent the carryover of impurities to the finished API. The maintenance of the purity profile mandates that a careful evaluation of process changes and potential alternate suppliers of solvents, raw materials, intermediates, and APIs be made. The analytical method development and synthetic chemistry skills required to obtain the necessary data on impurities meeting the FDA's criteria are substantial. These efforts are well rewarded in an expanded knowledge of the process chemistry and analysis that can ensure the quality of the desired active moiety.

C. Vendor Support to Validation

A frequent practice in API production is the subcontracting of certain chemical steps to outside suppliers. As is the case with subcontracted production for dosage forms, the owner of the NDA or the drug master file (DMF) maintains responsibility for the validation of the process and must secure the cooperation of the subcontractor in the performance of any supportive qualification/validation activities. Agreement to this arrangement should be a precondition to the awarding of the contract to the supplier.

D. Supplier Quality Evaluation and Audits

Suppliers of intermediates, reactants, solvents, and other materials should be subjected to the same types of evaluation utilized for other dosage forms. The extent of the assessment should vary with the importance of the material to the process. Precedence would be given to those materials whose purity would have an increased impact on the finished API. Where the material being produced by the vendor has a direct impact on the API's quality, as would be the case for chemical intermediates, a more intensive approach is required. Periodic audits of these key suppliers should be part of the overall quality assurance program.

E. Sampling Plans

Obtaining samples of finished APIs or their intermediates presents the same difficulties encountered in the sampling of any similar material. When samples are taken of powder or crystalline materials, questions regarding the uniformity of the material being sampled must be addressed before the results of the sampling can be considered meaningful. APIs that are dried in rotary or fluidized bed dryers may be blended sufficiently as a result of the drying process. However, where tray dryers are utilized, a final blending of the dried material may be required before sampling for release to the next stage of processing. In certain instances an intermediate or finished material will not be isolated as a dry powder but will be released as a solution in an appropriate solvent. Under these circumstances concerns regarding the sampling of the material are minimized.

F. Particle Sizing

Milling and micronizing are common activities in the final stages of API manufacture. These procedures are utilized where the API producer has committed to providing a particular particle size for use in the formulation. Given the importance of particle size in many final dosage forms, where present, these processes should be validated. Control of the final particle size for the finished API should not rely on the milling/micronizing step alone. Control over the crystallization procedure is generally necessary to minimize the variation in the material that is to be sized in the mill. It should not be assumed that the milling/micronization procedure will be tolerant of a wide range of in-feed materials and still provide a consistently sized finished API product. The uniformity of materials is sometimes improved by passage through a particle-sizing procedure or sifter, but this step alone should not be considered sufficient to achieve a uniform mix of the material prior to sampling (see the section "Sampling Plans").

G. Reprocessing

There is occasional need to reprocess an intermediate or finished API in order to alter its crystal size, reduce impurities, or otherwise recover off-specification material. Where these processes are utilized, their inclusion in the validation program is essential. FDA requirements on reprocessing and reworking of materials require the validation of any material reclaimed in this fashion. This is most readily accomplished as part of the developmental process.

XI. CLEANING VALIDATION

A comprehensive discussion of cleaning validation is beyond the scope of this chapter; the reader should refer to other sources on cleaning validation for details of this activity (22–24). Within the context of this chapter, only those aspects of cleaning validation unique to API production will be presented. Additional guidance can be found in FDA's *API Inspection Guide* (6).

It should be noted, however, that cleaning effectiveness has become an area of much greater concern in recent years, especially for multiuse equipment. These concerns become greater for unit operations closer to the final isolation and purification of the API but are still significant in the earlier reaction steps. While the debate continues over the acceptable level of the carryover from one campaign to the next, most firms have established cleaning acceptance criteria that are difficult to satisfy with the traditional chemical-manufacturing equipment used throughout most of the industry. The cleaning methods and practices described later often require multiple iterations to reach acceptable visual and chemical test limits. Newer facilities are beginning to incorporate design criteria to enhance cleanability. For example, final isolation, purification, and drying steps may use equipment identical to drug product manufacture. Even reactors and piping, if not truly sanitary in design, are incorporating many of the cleanability concepts used for drug products. These include fewer fittings, elimination of screwed fittings and flanges, better surface finishes, and more easily cleanable valves.

A. Boil-Outs

Commonly used to clean API equipment, boil-outs entail the introduction of the solvent (it could be water) used in the just completed process and heating it to reflux. The expectation is that the evaporation/condensation will result in the dissolution of any residue on the equipment in the solvent. This will remove it from the internal surfaces that are ordinarily inaccessible for direct cleaning and thus clean them. Boil-outs are also utilized as one of the last steps in preparation of equipment for the start of a process or campaign.

B. Lot-to-Lot Cleaning

As the production of APIs often requires that solvents and materials with substantial toxicity be employed, cleaning of the equipment after completion of the process has the potential for exposure of the worker to those materials. For this reason, it is common in API facilities to include some basic forms of waste treatment and equipment cleaning directly in the process in an effort to minimize worker exposure later. In addition to these measures, many processes include the reuse of equipment and retention of materials in the equipment without cleaning. A typical instance would be leaving a heel in the centrifuge at the completion of the batch, thereby eliminating cleaning of the centrifuge after each batch. The retention of the heel must be validated, as it represents a portion of the first batch, which may now become a part of subsequent batches. In fact each batch in the entire campaign is potentially mixed with material from every prior batch! In this manner, the amount of cleaning required between batches of the same reaction step would be reduced. In those facilities where a process train is essentially dedicated to the same reaction step over a long period of time, the equipment and process are specially designed to minimize batch-to-batch cleaning of the equipment. There are of course instances where the presence of even trace quantities of finished material at the start of the reaction may create an undesirable outcome; in those circumstances the equipment must be cleaned after the completion of each batch. Sparkler and other filters used to recapture catalysts, activated carbon used for decolorization, and by-products may require cleaning after every batch.

C. Campaigns

The production of a number of batches of an identical synthesis in the same equipment is common in the manufacture of APIs. As mentioned earlier in relation to the qualification of equipment, production in a campaign mode may require the partial reconfiguration of the equipment train to allow for a new campaign. This may be a reaction leading to the same or a different API. To allow for campaign usage, the extent of cleaning required will generally be far greater than what is carried out between batches of the same process step. Cleaning limits for campaign cleaning are generally tighter than those applied for batch-to-batch cleaning. It is beneficial in campaign cleaning to follow a defined plan for changeover from one product to another.

D. Sampling for Residuals

In order to determine whether a piece of equipment has been appropriately cleaned, sampling is performed. Here again, the particular nature of the API materials makes for a more difficult situation. In dosage form manufacturing, relatively few of the materials likely to be retained on the surface of the equipment pose any substantial risk to the worker. In those dosage form processes where toxic or potent materials are handled, the design of the equipment with smooth surfaces, rounded corners, sanitary fittings, etc., reduces cleaning difficulty. The same equipment design principles make sampling of pharmaceutical equipment relatively simple due to provisions for access and inspection. The bulk of API equipment is designed to operate under more aggressive conditions and cannot always integrate the design features so commonly found in its pharmaceutical counterparts. Moreover, worker safety becomes a far greater concern, as the solvents and materials are not conducive to direct exposure to the employee. Sampling of API equipment may be restricted to fewer locations, and those locations may not be in the most-difficult-to-clean or "worst-case" locations. For this reason, the residual limits for APIs may need to be far lower to accommodate the uncertainty of the sampling that can be performed.

XII. COMPUTERIZED SYSTEMS

The application of computerized systems in the pharmaceutical industry is perhaps greater in API processing than in any other. Distributed control systems (DCS) have been utilized for many years in the control and regulation of chemical process plants. Their adaptation to API preparation is straightforward. The validation of computerized systems in the pharmaceutical industry has been extensively discussed, with the constant recognition that their extensive usage in API production was a given (25,26). Industry and regulatory guidance having always recognized this fact, this chapter could not hope to do justice to the subject that has filled several textbooks on its own. The reader is encouraged to follow the recommended practices of Parenteral Drug Association (PDA), Pharmaceutical Research Manufacturers Association (PhRMA), and good automated manufacturing practices (GAMP).

Process Analytic Technologies are becoming of increasing importance in dosage form manufacturing as a consequence of FDA encouragement (27). Those trained in process control see these as little more than adaptations of methods chemical engineers have utilized for years in continuous processing. Their application in API production is certainly possible, and will likely be facilitated by the familiarity the professional staff has with both automation and process control.

XIII. PROCEDURES AND PERSONNEL

Where computerized systems are not utilized for the execution of the chemical synthesis, the chemical operator, following detailed batch records, is responsible for the operation of the equipment. The batch records must provide for sufficient detail to ensure that the worker can safely and properly perform the desired actions. In certain larger process trains, more than one operator will work simultaneously on the same batch. Provided that there activities are closely integrated, there is little problem with this type of approach. The personnel must be trained in their jobs, and records of the training must be retained by the firm.

XIV. VALIDATION OF STERILE BULK PRODUCTION

The preparation of APIs that must be sterile on completion of their synthesis and purification is a common activity in the pharmaceutical industry and increasingly common in biotech processes. The validation of sterile APIs represents one of the more difficult activities in the entire spectrum of validation. Not only must the final material meet all of the physical and chemical requirements associated with other APIs, it must also be free of microorganisms, endotoxins, and particulates. In doing so all of the considerations for validation of APIs outlined in this chapter must be addressed, with added concern for sterilization, environmental control, aseptic techniques, and other subjects associated with the production of sterile products. This subject has been addressed in a separate chapter in this volume.

XV. CONCLUSION

This chapter has provided an outline of validation considerations relative to the production of BPCs. This is a subject that has only recently become of interest to the pharmaceutical community. The authors, while familiar with both validation and bulk pharmaceutical processing, have undoubtedly mentioned any number of issues that may not yet be embodied in validation protocols within operating companies. We have included these issues to ensure completeness in the presentation, not to suggest that they be included in every validation effort. As time passes, the industry will gain experience with the validation of APIs and will perhaps exclude some of these issues, while including other aspects we have not identified. Our intent in this effort has always been to integrate common validation practices with the unique aspects of bulk pharmaceutical manufacturing. By no means do we expect this to be the definitive effort on this complex subject. The reader is encouraged to monitor industry and regulatory developments relative to API validation as substantial changes in cGMP requirements for APIs appear likely.

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8 Quality of Active Pharmaceutical Ingredients

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I. INTRODUCTION

The quality of active pharmaceutical ingredients (APIs) intended for development and commercial products is defined as meeting the appropriate specifications for the APIs and being produced in an appropriate facility. Requirements for this type of API can be found in International Conference on Harmonization (ICH) guideline Q7 and the Food and Drug Administration's (FDA) current good manufacturing practices (cGMPs) regulations. Most countries regulate the manufacture of these types of APIs. These regulations require a total systems approach to ensuring an API has the appropriate level of quality. Current guidelines and emerging regulations now indicate that the control of API quality should start with the manufacturing of material intended for the first preclinical toxicology studies. In early development, the applicable regulations and guidance are limited to a brief section within the FDA's Good Laboratory Practice (GLP) regulation, 21 CFR 58, and internationally in the nonbinding Organisation for Economic Co-operation and Development (OECD) GLP guidelines. As the regulators continue the refinement of requirements for early-stage API and drug product candidates, it makes good business sense to ensure that all components in the quality system are properly designed, validated or qualified, maintained, and operated to ensure the API consistently meets quality requirements for the corresponding stage of development. The general components of the system are the process, the facilities, and the people. This chapter addresses these components in the context of the domestic and international regulatory landscape, including ICH guidelines Q9, "Quality Risk Management," and Q10, "Pharmaceutical Quality System," and the FDA's guidance for the industry, "CGMP for Phase 1 Investigational Drugs." These newly developed guidelines, resulting from an international effort of concerned pharmaceutical manufacturers and the associated regulators, have required companies to reexamine their policies, management's responsibilities, and how risk is measured and managed across all phases of development and commercialization.

II. THE PRODUCT

To determine the appropriate API quality, we must first introduce the concept of "intended use." This concept recognizes that the quality of the API varies depending on the stage of development. The quality of the API may be different if the "intended use" is toxicology studies versus an API intended for clinical studies and a commercial drug product. The "intended use" concept is based on good science and a realistic approach to risk management regarding the degree of investment in knowledge and controls over the API candidate and its stage in the developmental process. In general, the quality improves and related controls increase as the API moves from preclinical studies to clinical studies and finally commercial products. The reason manufacturers take this strategy is directly linked to the pressures of bringing new products to the market in the shortest period of time possible. By conducting the toxicology and clinical studies before the API is fully developed and the process fully validated, manufacturers dramatically reduce the time needed to bring new products to the market. Also, since the vast majority of new compounds never make it through the development process, the strategy limits the investments they make in each compound.

Until recently, regulatory agencies around the world paid very little attention to the early stages of development, and even now, they rarely perform inspections. However, the current landscape of regulations and regulatory expectations is moving steadily to earlier stages of development, with a common theme of learning as much as possible about the API in early development.

In the absence of regulations that provide sufficient direction for early development, one of the most influential guidelines is ICH Q9, "Quality Risk Management," published as stage 4 guidance on November 9, 2005. This guideline lays out the concepts of risk management and describes the tools manufacturers can use to determine the appropriate quality and controls that should be built into processes. Although not specifically designed for early development, the tools outlined in the guidance can easily be adapted to each stage of development. According to ICH Q9: "It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm." As a result, it is up to each manufacture to assess each API and determine, for its intended use, what attributes are important based on the risk they represent to the preclinical and clinical studies and the patients taking the product.

With these concepts in mind, the quality of an API is determined by two factors, its conformance to preestablished specifications and whether it is produced according to a documented and, where required, validated process in a cGMP-compliant facility.

In early development (GLP studies) the main risks associated with API quality are consistency and adequate characterization. A manufacturer's standards at this stage of development should focus on understanding which properties of the API should be measured. In general, ICH Q6A, "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances," published as stage 4 guidance on October 6, 1999, provides direction as to which parameters should be measured. The parameters chosen should be those that might be changed during API development, which may also have an impact on the conclusions of the toxicology studies. At this stage of development it is often advantageous to not manufacture ultrapure API. Manufacturing API that contains expected process and product impurities at levels above what will be expected for the commercial API gives the scientist opportunities to examine the worst-case API during the safety studies. However, it is important that changes in the process be detected and managed, as they may render the preclinical studies invalid for support of an Investigational New Drug (IND) application.

Once the API reaches phase 1 in the development process, the manufacturer must ensure the API possesses appropriate chemical and physical attributes to ensure it delivers the intended pharmacological effect. The chemical attributes describe the appropriate purity and impurity limits. Impurity specifications are established from preclinical toxicological studies and are also based on reasonable minimums expected from regulatory authorities and consumers.

The physical attributes describe the necessary characteristics for reliable pharmaceutical processing into final dosage forms. These attributes are determined by empirical evidence from formulation trials to produce uniform and stable dosage forms of adequate bioavailability.

III. THE PROCESS

The synthesis and preparation of APIs for early development, for example, GLP studies, is often described in a lab notebook. During this stage of development, the main concern is associated with avoidance of contamination and documentation of the synthesis to ensure the API can be reproduced. To ensure these risks are adequately addressed, manufacturers should establish standards for maintaining laboratory notebooks, which should include proper identification of starting materials, people, equipment, and synthesis.

Once development is completed and approval is obtained, the expectation is that the quality of the API is designed into the molecule through the development of the full manufacturing process, from the laboratory-scale synthetic process to the end product. The synthetic process must be designed to minimize impurities, especially those that prove difficult to remove in the last step. Thus, through effective process development, yields are maximized, waste is minimized, and impurities are not formed, eliminated, or certainly minimized. The specific controls used by the developmental chemist to produce the high-yield, high-quality product must be documented; this documentation forms the basis for the proof of concept and for the validation report. In nearly all countries today, regulatory authorities require the API to be produced from a documented process that will reliably meet all appropriate specifications. This was strengthened by the issuance and adoption of the ICH tripartite guideline Q7, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients." The European Union (EU), the Japanese Ministry of Health, and the U.S. FDA adopted the guide.

IV. THE FACILITIES

The facilities in which APIs are produced are also addressed in this chapter because a component of the quality of an API is that it be produced in cGMP-compliant facilities. Those components of the facility governed by cGMPs are therefore part of this chapter. The essence of cGMPs for facilities or, for that matter, any aspect of API manufacture is that the facility performs as designed to ensure the quality of the product. Further, the performance characteristic must be documented, and management must demonstrate the facility continually performs as designed. Performance control monitoring, preventative maintenance, and carefully controlled and approved repairs or changes to facility components are all considered part of ensuring the quality of APIs.

The balance between good business and the investment we make in these controls will depend on the intended use of the API. During the early stages of development, when companies are usually conducting GLP studies, the primary concern is to ensure the facility is designed and managed to limit the possibility of contamination or material mix-ups. Often, an API manufactured for GLP studies is manufactured in laboratories on lab-scale equipment, primarily intended for process development. In these situations, general procedures should be implemented to direct the cleaning of equipment and to direct how the facility should be managed when production of GLP materials is scheduled.

As product development moves to the clinical phases, ICH Q7, "Good Manufacturing Practices for Pharmaceutical Ingredients," suggests that "during all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use." These procedures should also include the management of materials to minimize the risk of contamination, cross-contamination, and mix-ups.

Consistent with the direction provided by the ICH, the FDA guidance "cGMP for Phase 1 Investigational Drugs" recommends the following:

- Sufficient space, a clean environment, and appropriate construction.
- Appropriate lighting, ventilation, and heating.
- Appropriate cooling, plumbing, washing, and sanitation.
- Appropriate equipment to maintain an air cleanliness classification suitable to the operation performed in the area—for example, appropriate air-handling systems (e.g., laminar flow hoods) to aid in preventing contamination and cross-contamination of the phase 1 investigational drug.
- Appropriate equipment that will not contaminate the phase 1 investigational drug or otherwise react with, add to, or be absorbed by the phase 1 investigational drug and that is properly maintained, calibrated, cleaned, and sanitized at appropriate intervals following written procedures. In addition, the FDA recommends that all equipment used be identified and documented in the manufacturing record.

Finally, as the product is moved to commercial distribution, the controls described above are all applicable; however, in this case formal (documented) evidence is expected to support the adequacy of cleaning, calibration, and maintenance procedures. For facilities and equipment, this means manufacturers are required to perform formal commissioning and qualification studies and implement formal change control for all alterations and changes.

V. THE PEOPLE

The people who produce the API, in all phases of development and commercial manufacturing, are considered a critical part of the system and, as such, become part of the requirements for quality of APIs. To do their jobs effectively and to ensure the quality of the API, they must be properly trained and equipped. Qualified personnel must conduct the training, and the equipment must be of proper design and function. The specific training should be driven by the regulations (GLP or GMP) associated with the intended use of the API, that is, nonclinical and clinical studies or commercial manufacturing, and the specific individual responsibilities often captured in training curricula. Consistent with the importance of training, regulators require manufacturers to maintain evidence that training has been effective. In most cases, this expectation can be satisfied by competency-based training, which requires manufacturers to document the ability of individuals to demonstrate new skills or knowledge. Further, it must be ensured that supervisors assign work only to individuals who have successfully completed their training. The supervisors of people manufacturing APIs must also be properly trained to do their jobs. Finally, there must be an adequate number of people to allow sufficient time to perform these responsibilities in a satisfactory manner. This last point is often overlooked or not properly ensured. Manufacturers must implement metrics that measure their practical capacity to ensure the appropriate number of employees is assigned to critical tasks.

VI. THE QUALITY MANAGEMENT DEPARTMENT

As in most any other manufacturing enterprise, there is a quality control and/or a quality assurance department. Today, these departments are usually combined into a quality management (QM) department. The role of the QM department has also advanced from having the "check-test-decide" responsibility to being a strategic partner with manufacturing and engineering to manage and improve the quality of the entire process and system. However, the extent of involvement and its responsibilities are significantly different depending on the intended use of the API being manufactured and controlled, that is, nonclinical safety studies, clinical studies, or commercial manufacturing.

In early drug development, consistent with GLP regulations, the quality assurance unit (QAU) of record will closely monitor the conduct of GLP studies and will be less involved in the manufacturing of the API. In fact, it is common for the QAU to only be involved in providing oversight for critical process steps and performing occasional process audits.

For APIs and drug products manufactured for clinical studies or commercial distribution, the QM department, through its quality assurance arm, still has the responsibility vested in it by regulations, to release all products for their intended use. The activities and responsibilities of the QM department are also a component of product quality. Most cGMPs require that the QM department be responsible for reviewing and approving production procedures, process changes, most reports, procedures, and controls deemed necessary to ensure the quality of the process and product.

Finally, the QM department must have adequate laboratory facilities available to it and properly trained and experienced people to effectively carry out its responsibilities.

VII. THE REGULATORY AUTHORITIES

Health authorities in every country regulate drug products. In most countries these regulations also include APIs. In early drug development, for example, animal toxicity and safety studies [i.e., good laboratory practices (GLP)] and especially clinical studies [i.e., good clinical practices (GCP)], the expectations for manufacturers require controls designed to avoid contamination and mix-ups and to ensure the API is well characterized. The intent is to ensure you can conduct reproducible experiments and build a solid connection between the results of the safety studies and a decision to move the product into clinical development.

As the product moves to the clinical development phases, the cGMP regulations require that a drug meet all predefined quality specifications—as explained later, those specifications and requirements are less rigid for early developmental studies. In addition, the API must be produced from a documented and well-controlled process. The process must be validated once the product is ready for commercial distribution. Further, if the drug, or API, is not produced and controlled according to the established process, then the drug is considered adulterated and therefore not fit for use or sale. The regulations address every aspect of drug product manufacture and essentially require that the producer have documented evidence of proof of control over any aspect that might affect product quality.

The regulators were deliberate in their use of the word "current" when the cGMPs were promulgated. This qualifier enables the agencies to continuously require that manufacturers maintain their facilities and processes at the state of the art, thereby always assuring the public that drug products are as safe and effective as possible.

VIII. THE REGULATIONS

The regulations that govern manufacturing of APIs for early drug development are limited to 21 CFR 58, "Good Laboratory Practice for Nonclinical Laboratory Studies," in the United States and outside the United States in the OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring. From a manufacturing point of view, both of these standards are consistent in their expectations. Specifically, both standards require controls designed to avoid contamination and mix-ups and to ensure the API is well characterized.

The production of APIs is regulated in most countries. The ICH guideline Q7, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients," was recommended for adoption at step 4 of the ICH process on November 10, 2000. This document was adopted by the following agencies, denoting its widespread acceptance:

- EU, adopted by CPMP, November 2000, issued as CPMP/ICH/1935/00
- Japanese MHLW, adopted November 2, 2001, MSB Notification No. 1200
- U.S. FDA, published in the Federal Register, Vol. 66, No. 186, September 25, 2001, pages 49028 to 49029

The production process and all tests and controls must be approved by the regulating government in which APIs will be used, and the facilities and systems in which they are produced must meet the manufacturing standards set down by the governing body. Thus, the quality of APIs is based on two components: meeting final quality specifications and being produced according to the regulated, approved process in a facility compliant with the appropriate manufacturing standards. It is important to note that *both* criteria must be met—final specifications *and* compliance to manufacturing standards. These two components will be dealt with separately in this chapter. It is also important to note that the approach toward quality described in this chapter should apply to any API regardless of the country in which it will be used or sold or whether or not it will be a regulated item. The approach to quality, described in this chapter, is based on sound scientific principles and good QM principles and applies to any API. In fact, these principles apply to the manufacture of any chemical that requires a high assurance of quality.

This chapter will deal with the chemical synthesis of APIs. However, all the principles and regulations also apply to other means of preparation, such as fermentation routes and extraction from natural sources.

Finally, since it is assumed throughout this chapter that the API will be subject to regulatory requirements, reference will be made to the regulations. If the reader is dealing with an unregulated item, such reference may be ignored, but consideration for the scientific principles on which the regulation is based should be seriously considered.

IX. PART I: DEFINING AND ENSURING THE QUALITY OF THE ACTIVE PHARMACEUTICAL INGREDIENT

This section addresses how to:

- define the necessary quality attributes based on each phase of product development,
- test for them,
- design them into the process, and
- validate the process to ensure consistent production.

As APIs are regulated articles, their quality is determined not only by satisfactory test results but also by the assurance that the process was conducted according to a validated process. However, as the API moves through development, for example, during GLP studies, the process and analytical methods will not be fully developed or validated. As a result, manufacturers must establish controls that will ensure the API quality and associated characterization are appropriate. Tables are included at the end of this section to illustrate the concept of "intended use" as a way of determining which controls are appropriate. The tables, which are divided into GLP studies and phase 1 clinical studies, depict the increasing rigor of possible controls as the product moves through development, balancing the needs of good science, good business practices, and regulatory expectations.

A. Defining the API Quality

1. During Development

During early API development, manufacturers are usually working to improve and simplify the manufacturing process to improve yields, remove or reduce impurities, and ensure the process is repeatable. However, during this time, material is needed to begin the toxicology and pharmacology studies necessary to eventually support an application with regulatory health authorities before clinical development can begin. During this stage of development, the focus is not with a particular level of quality. Instead, manufacturers need to ensure the API is well characterized, contamination is avoided, and documentation is sufficient for the product to be reproduced. The goal of the characterization is to make sure major changes in the API or impurities can be detected. This will ensure safety studies will effectively support a decision to move the development into clinical phases. This process continues during the clinical phases; however, changes to the manufacturing process or the analytical methods must be controlled to ensure the impact on patient safety and the manufacturing of the API are well understood and approved before the changes are made.

2. During Commercial Manufacturing

Before the API is ready for commercial manufacturing, it must have its final chemical purity and impurity and its final physical attributes specified; some articles also require microbiological analyses to be determined, depending on the final dosage form and the manufacturing process involved. These attributes are established to ensure the API will perform satisfactorily in the pharmaceutical manufacturing process and will result in a final dosage form; that is, the drug product that will meet its initial release specifications and final stability requirements. The chemical purity minimum is usually set at 98 percent to ensure proper dosing in the drug product and to ensure a minimal amount of impurities. The physical parameters should be established with knowledge of the pharmaceutical process and the ultimate final dosage form. Other attributes usually include color of the solid form and/or a specific solution, melting point, specific rotation if optically active, crystal morphology if important for the drug product, and so forth. A list of typical API specifications is provided in Appendix 1, along with a rationale for each one.

When setting API physical attribute specifications, the most important aspect to consider is the use of the API in the pharmaceutical process; namely, whether it will be wet for granulation, dissolved for solution, dry-blended, and so on, and the type of drug product to be made: tablets, capsules, solutions, sterile or nonsterile, or other. It is also important to know how the drug product will be used by the patient; for example, if it will be used as a powder blended with other excipients, careful consideration should be given to particle size and distribution, rate of dissolution, and the eventual color of solution (for aesthetic reasons) when dissolved by the patient (or health care giver) prior to use. For this reason, final API specifications are always defined with the cooperation of the pharmaceutical development area. The quality assurance function approves final API quality standards, taking into consideration all requirements: process related, governmental, and customer.

3. Testing the API During Development

As we discussed earlier, during drug development, many of the specifications that define the API have not been finalized and the analytical methods used for testing have not been fully developed or validated. From a product quality perspective, it would be ideal for all of the methods and specification to be finalized before we use the material in safety or clinical studies. However, the time and resources needed to make this happen would be prohibitive and not a good use of those resources. A better choice is to use a risk-based approach to determine which tests are necessary to ensure the API is well characterized, that is, the chemical and physiochemical properties, as well as impurities, are identified. The goal should be to conduct sufficient testing to detect major changes in these properties and that the methods used are reliable enough to make these decisions. As examples, we have provided tables at the end of this section to demonstrate the types of controls that can be considered to accomplish this goal.

4. Testing the API for its Defined Attributes

Each quality attribute required of the API must have a sound and proven test procedure. In regulatory compliance terms, this means the test must be validated; that is, to have documented proof that it performs reliably is indicative of the attribute under question and is not biased by interfering components. There are eight specific components of a validated test, and for an excellent treatise on this, the reader is referred to the current USP or the ICH guidance on analytical test validation. Most regulatory authorities require a test for all significant API quality attributes on each lot produced. In nearly all cases, the pharmaceutical manufacturer requires a certificate of analysis (CoA) documenting the results obtained on each lot, as well as a statement from the quality unit that the batch met its established quality criteria.

B. Designing Quality into the Process—Chemical Synthesis

As described earlier, the pharmaceutical manufacturing process and end use of the drug product dosage form is the basis for establishing the limits of chemical purity and physical attributes. Having predefined these attributes, the synthetic chemist and chemical engineer have the task of *designing quality into the process*, thereby ensuring every lot will meet its criteria. This is perhaps the most significant aspect of chemical process validation and a cornerstone of most regulatory requirements for quality assurance. After the chemical process is developed, a technical document, which explains how and why certain reagents, steps, controls, etc., were chosen in order to build quality into the product, should be prepared. When the manufacturing team takes on the commercial implementation of the process, and goes through the formal manufacturing validation process, it should rely heavily on this technical document to prove the quality of the final API. As stated in the introduction, quality is designed into the process not for regulatory purposes, but because it makes good manufacturing and business sense to do so. Manufacturers want a process that safely and reliably delivers high yield and quality for economic and environmental reasons.

One should begin the approach to designing quality into the API with the concept of designing a perfect system. Keep in mind that all the safety, environmental, and economic reasons for developing a perfect chemical synthesis are precisely consistent with the goal of designing quality into the process and very well serve all regulatory process validation and control requirements. If one imagines a perfect process, there will be no toxic emissions about which to be concerned—no safety concerns or the need for special safety controls—and the yield of each step will be 100 percent of the desired intermediate, stereo isomer, and end product. Such a process would be free of any impurities and would assay for 100 percent purity. The next challenge is to design the synthesis so that each step can be precisely controlled to always provide the same end result. The design work requires a complete understanding of the chemical reactions in the synthetic process under development. Then a clever design can be developed to eliminate any undesirable side reactions. In some instances this can be achieved by sophisticated use of functional group–protecting agents and in other instances by changing the sequence of functional group introduction onto the end product–building block and sometimes by simple careful control over reaction parameters. Once the process has been perfectly designed, developed, and controlled, the last concern is over the control of quality and reliability of the raw materials, proper functioning of equipment, and error-free operations by personnel. With the vision of a perfect system in mind, one can imagine how the API quality would be perfect and consistent.

C. Validation of the Process

This aspect of the regulations is perfectly aligned with business interests. The regulations require that a chemical manufacturing process be validated, which the author personally defines as "proof of knowledge of control."

While the term "validation" has various definitions in several different regulations (cGMPs), all essentially mean or imply "proof of knowledge of control." In essence, the validation of the process is the description of the process after all development work is completed, with the elaboration of the proof of synthetic pathway, controls over process conditions, and finally, sound analytical proof of quality from samples obtained during actual manufacturing campaigns in the plant. Critical process parameters such as time, temperature, and mixing conditions should be defined, controlled, and monitored. The kinetics of the synthetic pathway is documented in a process manual. The establishment of a process manual for each API is the foundation of process validation. In this manual, one describes *proof* of the *knowledge* of the process and the *controls* necessary for consistent results. Hence, the scientific design process to build the perfect process requires full knowledge of the chemistry of the process. That knowledge is described in the chemical pathway from raw materials to the final API. The scientific evidence, such as intermediate structure elucidation, spectrographic analysis [infrared (IR), near infrared (NIR), mass spectrometry (MS), ultraviolet (UV), nuclear magnetic resonance (NMR), carbon nuclear magnetic resonance (C13NMR), etc.], and the proposed chemical mechanism for each transformation, serves as the proof of that knowledge. Finally, during the course of the process development, full knowledge is gained concerning those parameters and conditions that affect the kinetics, yield, and purity of each step. Experiments to optimize each step for purity and yield lead the process engineer to describe the necessary controls and conditions. These controls are described in a process manual and are used in the scale-up work and ultimate full-scale operation in the chemical plant.

D. Reality

We realize that the perfect synthetic process will, in all likelihood, be too elusive. Eventually we must make the decision to focus our resources on the best process available after thorough development work yields a sound and reliable process. Each synthetic challenge represents reality of the business of API manufacturing, and so at some point, the feasibility of further studies versus commercializing what has been achieved to date must be evaluated on a risk (losing precious time in the market) to reward (achieving a superior process) basis. Suffice it to say here that to ensure quality of the final API, the validation of the process provides the necessary information to design in-process controls needed to monitor the progress of each step. These controls are the chemical and physical monitors that inform the operator that the synthesis is proceeding according to the original design. They are used also to inform the operator when the reaction is complete and when the next step may occur. In many cases, especially when the process is well defined and designed, including the quality of starting materials and reagents, a good control is simply the use of time, depending on knowledge of the kinetics of the reaction.

In-process controls should always be "in the process," that is, "online," and not requiring a sample to be withdrawn and sent to a laboratory for testing and evaluation. Under some conditions, it may be necessary to take samples, but this should be avoided whenever practical.

In-process controls are probes, or monitors, inserted into the reaction vessel or the gauges that measure and record pressure and temperature of vapors above the reaction medium. The attributes that are measured include a wide variety relevant to the specific chemistry taking place. Properly established tests, for example, IR or UV analysis, can predict the end point of a reaction by following the disappearance of a functional group on a reagent or the formation of one on the molecule being produced. Monitoring the presence of any side products, such as water or gases, will signal the end point of the reaction when their theoretical yield is obtained.

X. PART II: THE REGULATIONS FOR QUALITY

A. The Emergence of Specific Regulations for APIs

1. FDA: Good Laboratory Practices

In the mid-1970s the FDA and some members of Congress had begun to question the quality and reliability of nonclinical studies being submitted by the pharmaceutical industry in support of New Drug Applications (NDAs). In 1975, the FDA investigated two pharmaceutical companies and uncovered serious problems with the conduct of safety studies submitted to the FDA. The violations included poor record keeping and data storage, inadequate personnel training, poor test facility management, and even fraud. In response the companies worked with the FDA to resolve the issues, and by January 1976, scientists at Searle had developed a guidance document they called "Good Laboratory Practice." Searle submitted the guidance document to both the FDA and the Pharmaceutical Research and Manufacturers Association of America (PhRMA). In December 1978, the FDA published final GLP regulations and made compliance with them the law in the United States in June 1979. These regulations were made part of title 21 of the Code of Federal Regulations (CFR), as part 58: "Good Laboratory Practice for Nonclinical Laboratory Studies," and they applied to all nonclinical safety studies intended to support research intended to support marketing authorizations of products regulated by the FDA. Further changes to the GLP rules were proposed in 1984, and in September 1987, the FDA published its final rule—"Compliance Program Bioresearch Monitoring: Good Laboratory Practices."

Within the GLP regulations, specific requirements are included for the use of APIs (i.e., test article), controls, carriers, and mixtures. In the preamble to the GLPs, the FDA concluded that "... characterization of test and control articles need not be performed until initial toxicology studies with the test article show reasonable promise of the article's reaching the marketplace." In arriving at this conclusion, the Agency also indicated that "... prior knowledge of the precise molecular structure of a test article is not vital to the conduct of a valid toxicology test." However, the FDA indicated it is important to know the strength, purity, and stability of a test or control article that is used in a nonclinical laboratory study. The stability may be determined either by stability testing before initiation of the study or through appropriate periodic analysis of each batch. Finally, the GLPs require manufacturers or testing laboratories to ensure all tests or control articles that are mixed with a carrier be tested for uniformity of the mixture and concentration. The FDA believes that knowledge of the dose of test or control article used in any test is essential for the proper evaluation of the results of that test.

B. International Good Laboratory Practices

Internationally, the OECD publishes the most widely recognized guidelines for the conduct of GLP studies. The OECD is an intergovernmental organization in which representatives of 29 industrialized countries in North America, Europe, and the Pacific, as well as the European Commission, meet to coordinate and harmonize policies, discuss issues of mutual concern, and work together to respond to international problems.

The OECD Principles of GLP were first developed by an expert group established in 1978 under the Special Program on the Control of Chemicals. The GLP regulations for nonclinical laboratory studies published by the FDA in 1976 provided the basis for the work of the expert group, which was led by the United States and comprised experts from the following countries and organizations: Australia, Austria, Belgium, Canada, Denmark, France, the Federal Republic of Germany, Greece, Italy, Japan, the Netherlands, New Zealand, Norway, Sweden, Switzerland, the United Kingdom, the United States, the Commission of the European Communities, the World Health Organization, and the International Organization for Standardization. Given the close collaboration between the FDA and the above-mentioned international regulatory agencies and organizations, it is not surprising that the U.S. GLPs and the guidelines published by the OECD are complementary and work well together.

C. Commercial API Regulations and Guidance

An active ingredient of a commercial pharmaceutical product must meet two distinct sets of criteria before it can be used for producing a drug product suitable for sale in most countries around the world. One set of criteria is the product specifications, addressed in the section "Part I: Defining and Ensuring the Quality of the Active Pharmaceutical Ingredient" of this chapter. The other set is the assurance that the product is produced according to cGMPs prevalent in the regulated market in which the drug product will be sold. Most countries have approved and enforced regulations for drug products; there were few with specific regulations for the APIs used therein. With the development and subsequent adoption of ICH Q7 by the regulatory authorities in Europe, Japan, and the United States, a consistent approach to cGMPs for the manufacture of APIs is now achievable.

The chapter is written as if the regulations are in force throughout the world. This position is valid, given the adoption of ICH Q7.

One final introductory comment before beginning a review of the ICH guidance: When describing "cGMPs," they are always prefaced by the adjective "current." Q7 acknowledges the equivalence of the terms "current good manufacturing practices" and "good manufacturing practices." The equivalence of the terms is deliberate. It requires that manufacturers continuously apply the current state of technology and practices when developing new drugs. In certain special cases, manufacturers will also be compelled to apply the new technology to older APIs and the processes, facilities, etc., whenever such application will play a significant role in assuring, or advancing, the end-product quality. Furthermore, since the "current" is part of the guidance, manufacturers need to be aware of such advances and make the necessary changes to their systems and facilities to remain compliant. Hence, the guidance is always considered updated to the current best practices without the need to return to the regulating bodies for approval.

This part of the chapter follows the format of the ICH guide as finalized by the ICH in November 2000 [available at: www.ich.org (see "Quality," then "Q7") or www.fda.gov]. However, it is not intended that this will represent a summary of the guidance. Instead, this text offers practical insight into the reasons and meanings of certain aspects of the requirements following its layout to facilitate a quick review and reference, should that be necessary. The reason for selecting the ICH guide is due to its widespread adoption, its comprehensive approach, and its high quality as a reference document.

The ICH guide is laid out in the following format to demonstrate the scope and extent of its influence on the entire manufacturing process (note we are following the ICH numbering format). Each of these ICH sections is discussed later.

1. Introduction
2. QM

3. Personnel
4. Buildings and facilities
5. Process equipment
6. Documents and records
7. Materials management
8. Production and in-process controls
9. Packaging and identification labeling of APIs and intermediates
10. Storage and distribution
11. Laboratory controls
12. Validation
13. Change control
14. Rejection and reuse of materials
15. Complaints and recalls
16. Contract manufacturers (including laboratories)
17. Agents, brokers, traders, distributors, repackagers, and relabellers (not covered in this chapter)
18. Specific guidance for APIs manufactured by cell culture/fermentation (not covered in this chapter)
19. APIs for use in clinical trials
20. Glossary

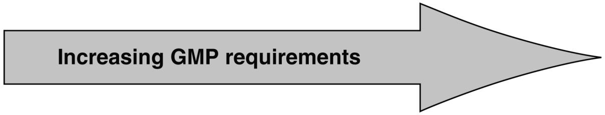
To ensure the manufacture of an API meets the requirements described in the ICH guide is, indeed, a significant task. It requires that all the requirements be understood by all appropriate people dealing with the manufacturing process, that their understanding be proven through documented records, and that there be effective systems and procedures in place to ensure that all appropriate steps, controls, tests, etc., are conducted, as described, in the product's marketing authorization application, in the firm's drug master file, and in the documented standard operating procedures of a manufacturing facility.

Let us begin with an analysis of the ICH Q7 guidelines, section by section.

XI. ICH Q7 SECTION I: "INTRODUCTION"

This section describes the scope and application of the guidelines. It provides guidance as to when cGMPs should be applied to the manufacturing process. Reproduced in the following is a grid from Q7, "Introduction." It shows the various types of API manufacturing technologies, for example, from "chemical manufacturing" on the top left of the grid to "classical fermentation" on the bottom left. For each technology, moving left to right, the likely processing steps that might be used are mentioned. As the process moves closer to the final steps, the degree of cGMP requirements increases. At some logical point, the heads of manufacturing and quality decide on the "starting materials" that will reliably produce the API. These starting materials must be very well characterized and always be tested for conformance to predefined attributes before use in the API process. Admittedly, which chemicals are defined as "starting materials" can be debated. Logically, if a reagent will become part of the final molecule, it is a very good candidate to be chosen as one of the starting materials. From this point forward, the cGMPs applied to the process increase in their stringency. Final packaging of the APIs will be very well prescribed in both the environmental requirements and in the labeling controls applied.

Type of manufacturing	Application of this guide to steps (shown in gray) used in this type of manufacturing				
Chemical manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of intermediate(s)	Isolation and purification	Physical processing and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/comminuting			Physical processing and packaging
Biotechnology: fermentation/cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing and packaging
“Classical” fermentation to produce API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging



A. Compliance Requirements

Defining the point at which cGMPs first come into effect for the API (or intermediate) being produced is the essence of this section. From that point forward, the strategy and the requirements for consistently producing APIs in conformance with cGMPs are developed.

XII. ICH Q7 SECTION 2: "QUALITY MANAGEMENT"

Beyond the principle that quality is the responsibility of all personnel, there are specific responsibilities that must be carried out by the quality unit. The challenge is to achieve a balance between executing the necessary activities and not allowing the abdication of other departments toward quality. The quality unit most often becomes a focal point for all quality-related matters, functioning as a technical consultant in quality and compliance. It is imperative that the quality unit be independent of the manufacturing operations in order to achieve an objective perspective. Some of the basic quality responsibilities include review and approval of documents (specifications, test methods), written Standard Operating Procedures (SOPs) for all departments, records (batch records and log books), deviations and their investigations/resolutions, and finally the release of the product to market.

Internal auditing (also termed "self-assessment" and "self-inspection") is also a cornerstone of QM. Knowledge of the plant and its systems can determine the annual schedule to be followed in conducting audits. Once executed, the information contained in an internal audit is useful not only for the department being audited to improve its operations but also for the plant on a larger scale to know about potential quality issues in advance of problems occurring. Senior management must be made aware of the issues found in internal audits since it is responsible for setting the strategy for the plant and can allocate resources to correct any deficiencies.

In addition to internal audits, which are carried out on manufacturing processes, a review of the product as it is manufactured, and its ability to meet specifications both initially and over time, can yield information for improving processes and the product itself. These reviews are typically captured in an annual report known as the "Product Quality Review," "Annual Product Report," or "Product Quality History." Each plant defines the scope of the report but minimally the results of all tests (at the time of release and when tested subsequently), the review of deviations and difficulties in its manufacture, and complaints received from customers, especially looking for trends that may not be apparent on a day-to-day basis.

A. Compliance Requirements

A well-defined internal auditing program, comprehensive in scope with a good communication plan, can help identify and prevent systemic problems in the operation. The internal auditors must have not only a thorough knowledge of the operations and the regulations but also the best means of achieving conformance without creating unnecessary bureaucracy. Combined with annual product quality reviews, opportunities for quality improvement should be identified for both the products and the processes.

XIII. ICH Q7 SECTION 3: "PERSONNEL"

No matter what API is made, there are always people involved in the process. It has been said by numerous CEOs, "People are our greatest resource." Each manufacturing operation needs the right level of personnel in terms of both number and qualification for each job in the operation. This presupposes that each job has a well-defined job description complete with training requirements and the demonstration of the proficiency of the necessary activities. While this has been common in the laboratories, companies are now expanding the concept of training and qualification to the informal programs common in our industry. The use of "mentors" exists in most manufacturing operations, but few ask: How are these mentors chosen, what are the skills that make one person an excellent mentor and the other a poor one, and what training is needed to make the mentoring effective and efficient? The recognition of mentoring as a training activity will increase the knowledge base resident in your workforce.

Since people are involved in the manufacture of APIs, their hygiene becomes important. The firm must provide adequate toilet, cafeteria, and changing/locker facilities. This achieves protection not only of the personnel but also of the product.

It is common practice to employ consultants or contractors for limited times on short-term specific projects. Consultants or contractors must follow the same requirements for personnel hygiene and must have the training necessary to perform their duties.

A. Compliance Requirements

All personnel involved in the manufacture of APIs and intermediates must have the necessary training, education, and skills to perform their activities in a consistent manner. This must be documented not only for regular employees but for contractors/consultants as well. Proper hygiene and sanitation protecting the product and the personnel must be part of normal operating conditions at the site.

XIV. ICH Q7 SECTION 4: "BUILDINGS AND FACILITIES"

In planning a facility, there are always drawings of the facility, equipment, utilities, material flow, and personnel flow. This is necessary to ensure that in the design of a facility, adequate space is provided for the material and personnel to flow smoothly and for the prevention of mix-ups and contamination.

Utilities can have a direct impact on the quality of the API. They can either be required to ensure consistent environmental parameters, as evidenced by heating, ventilation, and air-conditioning (HVAC) or by providing materials that come in direct contact with the product (e.g., compressed gases). Inconsistency in either of these functions can result in inconsistent quality of the product and/or process. As such, all utilities having a direct impact must be qualified through proper design and rigorous testing to show they will consistently perform as expected. In addition, these utilities have to be monitored to ensure they are continuing to function as necessary.

Water can be used for a variety of purposes within the manufacturing of APIs. Because of the many differing uses, such as a cleaning material or a raw material in the manufacturing process, how the water is used will determine the specifications to be developed. Beyond how the water is used, the product it is used in will also determine the specifications. At a minimum, process water must meet the World Health Organization (WHO) guideline for drinking (potable) water quality. If this water is then treated to yield a water of a predefined quality, that process must be validated and the water produced monitored. This can include specifications for the microbial content and/or endotoxins in the water for an API to be used in a sterile product.

Containment considerations must also be built into the design of the facility and its utilities in order to protect the workers from adverse exposure to the API or its intermediates. Certain APIs are highly toxic or potentially deleterious materials, such as penicillin and cephalosporins. The side effects from these drugs can be life threatening. It may be necessary to develop separate and dedicated facilities for the manufacture of these types of compounds.

Lighting should be sufficient for all personnel to perform their activities without eyestrain. Certain APIs may need to be protected from light. In those cases, the lighting may have to be designed, taking into account the product's requirements and the personnel's needs.

Every operation will generate waste. In the case of the manufacturing of APIs, this waste can cause contamination throughout the manufacturing facility, if not removed in a sanitary and safe manner.

How a facility is maintained is one of the first indications as to whether a quality culture is resident at a site. A high-quality API requires a facility that is clean and free of pests and has utilities that function reliably. The cleaning agents or other materials used to maintain the facility of equipment must be known not to contaminate the product in its usage. A well-defined and executed preventive maintenance program can ensure reliability of the utilities.

A. Compliance Requirements

Engineering drawings detailing the facilities layout, equipment location, room usage, material flow, personnel flow, and utilities must be maintained to reflect accurately the building and facility. Procedures for the maintenance and monitoring of all the utilities that can impact product quality must be written and approved. Utilities producing materials that are used in the actual manufacturing operations must have specifications for those materials. Safety of the personnel and the prevention of the product contamination must be thought of in advance and captured in standard operating procedures specifying sanitation, containment, and refuse disposal practices. The maintenance of the facility, the building, and the utilities must be defined in operating procedures using materials that will not adversely affect the product.

XV. ICH Q7 SECTION 5: "PROCESS EQUIPMENT"

For each manufacturing operation there will be equipment either fixed or mobile to be used in the process. Sometimes the equipment may be placed outside the building itself. Equipment can be either closed (preferable) or open. If the equipment is not closed, there must be special attention to prevent contamination of the product. In either case, the equipment must be constructed of the right materials to ensure it can be easily cleaned and maintained. It must protect the product it is manufacturing and not affect the quality of the product. Identification of the equipment (and processing lines) is necessary to ensure traceability of the product to the equipment used. Not all equipment will need to be identified; each facility must define which pieces of equipment are considered major in their own manufacturing processes. The use of lubricants or other manufacturing materials is often necessary; however, when used, these materials must not contact the API or alter the specifications of the API.

A clean, well-maintained building is only half of the picture. A clean facility with broken or rusty equipment is just as indicative of a poor quality culture as is the reverse. The equipment in the building must be maintained in a good state of repair and cleanliness. The expectation must be that once processing starts, all the necessary equipment will function properly.

Cleaning materials must be chosen not only to clean the equipment but also to leave no residues, which may affect the quality of subsequent batches. How long a piece of equipment remains "clean" after cleaning is completed is an important factor to be considered in designing the cleaning program. Also part of a comprehensive cleaning program is whether reduced cleaning can be used for campaign manufacturing (subsequent batches are produced of the identical API).

Manufacturing equipment often provides data, information, and output, which can be used to determine the acceptability of the processes and/or the product itself. We must be able to rely on this data as correct and accurate. Therefore the analytical components of this equipment must be calibrated using standards whose authenticity is ensured. The time in between calibrations will be based on the reliability of the equipment and the criticality of the data. When calibration requirements are not met, decisions based on the data may be erroneous and must be revisited. Instruments that do not meet calibration requirements should not be used, and there must be an investigation to assess the impact on batches produced in that equipment.

Computerized systems are specialized pieces of equipment, which must meet all the requirements as other pieces of equipment. A logical application of the cGMPs should be applied in conjunction with special requirements such as 211 CFR Part 11, Electronic Records; Electronic Signatures. Validation is required; however, the depth and scope of the validation is dependent on the computerized application. The degree of validation may be dependent on the source of the computer system: commercially available software requires little validation, while software developed for a specific manufacturing step will require extensive validation. Once validated, the computer system must be maintained in a state of control. After all, it is still a piece of equipment, albeit highly specialized.

A. Compliance Requirements

Procedures for the cleaning, maintenance, and operation of each piece of major equipment must be developed and approved by the quality organization. There also need to have engineering drawings of the equipment, along with the maintenance of a revision history of these drawings. Many firms see engineering drawings analogous to documents and require quality approval of changes.

XVI. ICH Q7 SECTION 6: "DOCUMENTS AND RECORDS"

In a sense, our industry prepares two products, the API that goes out the door and the paperwork that records how this product was made. The paperwork consists of documents such as procedures, specifications, methods, and manufacturing instructions. These documents are prepared and revised by a formal change control process the quality unit must review and approve. The issuance of these documents to the operators, technicians, and other persons using these documents must be done in a controlled manner, ensuring they have the most recent (and only the most recent) version of the approved document. Typically, the quality unit has a documentation center, which will store the superseded documents and the approved master copies. The storage of documents must be defined in a records retention policy consistent with cGMP requirements (at least one year after the expiry of the batch or for APIs with retest dates, three years after the complete distribution of the batch) and any legal requirements of the firm.

The data detailing the actual manufacturing conditions (temperatures, lot numbers of starting materials, etc.) are recorded on a batch record. Data detailing equipment usage and conditions are similarly considered to be a cGMP record. Changes to cGMP records must show the person making the change and the date the change was made. Many firms also annotate the correction with the reason for the correction.

Only accepted raw materials may be used in the production of an API. This sets into motion a requirement for proper documentation surrounding the receipt, testing, acceptance, and release to manufacturing. Imagine that a raw material is found to be defective after it has been used in a product. The firm would have to trace (using the lot number of the supplier) to determine which batches this defective raw material has been used in. The records then must include the supplier's lot number, a unique lot number assigned to the materials, date of receipt of the material, and records of the testing and release of the material.

Manufacturing instructions are documents detailing the process and the controls necessary to produce uniform quality batches time and again. In a sense, the manufacturing instructions are the recipes for making the API.

Specific requirements for these records include the following:

- Name of the API and any unique identifying code.
- List of raw materials and the quantity or ratio of materials to be used. Specific calculations must be included as part of the specific batch record.
- List of equipment to be used.
- Specific production instructions in the correct sequence, with all necessary control parameters, time limits, yield ranges, and in-process control testing and specifications.
- Instructions for storage.

There should be a master batch record document from which each individual batch record is generated. This ensures that each lot made is manufactured following the same recipe. When the lot-specific batch record is issued, there must be a check to ensure that the issued batch record is specific for a single unique batch number and the instructions are identical to the master batch record document. The lot-specific record will have the signature of those individuals who performed critical processing steps in the manufacturing process and those who performed any in-process testing.

Eventually, irregularities will occur. Chemical manufacturing processes are a complex interaction of reagents, solvents, machines, and people. Machines can break down, and people can make mistakes. In-process materials or products do not always meet specifications. Each firm must have a system in place to identify and assess the impact of these deviations on product quality and process robustness. When deviations occur, they must be addressed as part of the batch record. Prior to the release of the batch, the quality unit must approve the deviations and how they have been resolved.

As the batch record details the executed processing steps, there are records for the laboratory testing for each batch. These requirements are completely consistent with the cGMPs for laboratory records for finished pharmaceuticals. Samples are taken to determine the acceptability of a material; the traceability of a sample to the portion of the lot where it came from must be known and recorded. We must know definitely what tests were performed on the sample (test method including revision date), what equipment was used to generate the data, who performed the test, and who reviewed the data (a second person must review the data), in addition to the acceptability of the test results themselves.

When the manufacturing and testing activities are completed, a review of the critical and noncritical process steps must be performed. The quality unit must review the critical process steps; the noncritical process steps can be reviewed by a different unit following procedures that have been approved by the quality unit.

A. Compliance Requirements

Any aspect of producing an API, from the receipt of all incoming materials from outside vendors right through to the last distribution of released material, must be appropriately recorded. Systems must be in place so that each specific lot of intermediate or API is reviewed and approved by the quality unit before being released. Effective systems need to be in place to both detect an unexpected result and then investigate it. Batch production records, or a sound sampling thereof, as well as all other quality-related records such as stability data complaints and so forth should be reviewed at least annually to ensure that in-process controls, procedures, and final product specifications are adequate and tightened, where appropriate.

XVII. ICH Q7 SECTION 7: "MATERIALS MANAGEMENT"

There must be a comprehensive system with procedures defining the receipt, identification, quarantine, storage, handling, sampling, testing, and disposition of materials. There must be predetermined specifications for materials purchased from a supplier, which has been approved by the quality unit. This presupposes there is a system for approving suppliers and the materials they supply. Critical raw materials must be identified, and changes to any specifications of critical raw materials must be handled under change control.

Selecting and monitoring suppliers has recently become front-page news, and regulatory agencies around the world are making it clear that more oversight is needed. One of the most recent cases involved serious injuries and deaths associated with the use of heparin, a blood-thinning drug that contained API from China. As a result, the FDA placed an import alert on shipments for the specified manufacturer and product. In February 2008, the importer of the tainted material, Baxter Healthcare Corporation, recalled all multidose and single-dose vials of heparin sodium for injection, as well as HEP-LOCK heparin flush products.

After launching an extensive investigation, FDA scientists identified a previously unknown contaminant in the heparin. The public reports revealed that the raw heparin, harvested from pig intestines on Chinese farms, was processed by small, unregulated, uninspected factories. These intermediates were then processed by larger Chinese packaging plants for export to the United States. The investigation also revealed that Baxter Corporation had very little knowledge of where the raw materials originated or which plants were involved in processing the materials. The lesson from this tragedy is clear: we must know which plants are doing what, properly inspect them, and follow up to be sure deficiencies are addressed.

A manufacturing plant will receive several different types of incoming materials; some require the strictest degree of controls (raw materials and intermediates, for example), while others can be handled with little more than good accounting practices (office supplies, etc.). For each material to be used in the manufacturing process, there must be a unique lot number assigned to the goods to ensure complete traceability to the supplier and the shipment. Shipping conditions can affect materials even during a short time; shipments of the same supplier lot number may require a different receiving lot number. Upon receipt, the containers should be checked for conformance to the labeling and be free from tampering or damage, which may cause contamination of the API. Before any material is used the quality unit must formally release the material.

The use of nondedicated tankers requires an additional level of assurance that cross contamination is prevented. This can be accomplished by audits of the suppliers and/or a certificate of cleaning supplied by the supplier and/or testing for impurities by the receiving firm.

Many firms rely on a CoA supplied by the supplier in lieu of actually performing required testing. This becomes a more proactive means of ensuring the quality of the material. Acceptance of a CoA is possible after a partnership is established with the supplier through a formal qualification and evaluation of the supplier's capabilities and reliability. Typically the process involves an initial questionnaire, followed by an audit by trained auditors and purchasing representatives. This helps determine if the supplier is qualified to produce the material consistently and in accordance with the firm's expectations. The material then needs to be approved for use in the manufacturing process; this is typically done with distinct batches produced by the supplier. The goal is to determine if the supplier's material performs reliably in the firm's manufacturing process. The entire process of qualifying vendors and the material they produce must be repeated on a periodic basis. For hazardous or highly toxic raw materials, full acceptance of the CoA may be warranted, pending a documented rationale.

It would be easy if all materials were received as a single lot in a single container; however, it is often the case that vendors will use multiple containers—and sometimes different lots, typically to facilitate their own handling and shipping efforts. Each container must be inspected at the time of receipt; however, the contents of each container need not be sampled and tested to determine the material's acceptability. The use of statistical sampling plans applied to each lot separately can help reduce the burden of sampling and testing, while still yielding a result representative of the batch as a whole. These sampling plans must take into account the number of containers received and the criticality of the material.

While these materials are held, either prior to release in inventory or in the manufacturing process itself, they must be held and handled so as not to contaminate the material themselves or other materials stored in the area. For example, heat-sensitive materials may need to be stored in a cool, controlled (i.e., data-recorded) location. It is quite common in API manufacturing to store materials outdoors. This can be accomplished for specific materials as long as the requirements stated above are met. When brought into the manufacturing environment, the containers may require an additional cleaning.

If a material is determined to be unfit for use and rejected, special storage and handling requirements must be met. It must be stored in such a manner that it cannot be used inadvertently in the manufacturing process. Many firms have designated locked cages to store rejected materials.

A. Compliance Requirements

The receipt, storage, and handling of materials must be performed in such a manner that there is complete traceability of the material to the supplier. Materials may be received against a CoA supplied by a qualified supplier in lieu of full testing. For this to happen there must be a formal supplier qualification process. For materials that are sampled and tested for release, there must be predetermined statistically valid sampling plans and acceptance criteria. Materials must be segregated or otherwise stored to prevent their use, until the formal release by the quality unit is granted. The materials must be stored in such a manner as to not compromise their quality attributes. Any rejected materials must not be used and must be stored in a separate area to prevent such an error. Rejected material should be returned to the vendor or otherwise properly destroyed.

XVIII. ICH Q7 SECTION 8: "PRODUCTION AND IN-PROCESS CONTROLS"

Earlier, the need for a master batch record document was discussed. This document describes the manufacturing instructions necessary to consistently produce batches of APIs that meet predetermined specifications. There will also be ancillary procedures, which will define all the conditions and their control parameters necessary to ensure consistency from batch to batch. Isolated materials should be labeled at each step in the process. This is true not just for the raw materials; as in-process materials are generated and isolated, the material's name, lot number, and status should be clearly labeled. As stated earlier, major pieces of equipment should be clearly labeled with a unique identification number and status, that is, cleaned and ready to be used, to be cleaned, or in use. If a processing step is determined to be a critical processing step, it may require witnessing of its completion by a second person, with the witnessing documented on the batch record.

Processing steps should have time limits—either a step must be completed within a certain time (e.g., mix for two hours), or an in-process material may be held for a specified amount of time. Deviations from these time limits must be addressed with a formal investigation as to the effect they may have on the quality of the product. The results and conclusions of the investigation must be documented.

The manufacturing process should be reviewed for those points where in-process testing can help ensure minimum process variability, thus achieving greater consistency in the yield and quality of the product. This review should ideally take place during development runs, but information from validation batches and annual product quality reviews can also be used. They can be valuable in determining which areas of the process or product should be more carefully monitored or whether process specifications should be changed. Types of in-process control tests include temperature of the process, pressure of the equipment, color of solutions, pH, and loss on drying. In-process control testing and specifications should be defined in documents approved by the quality unit.

Each intermediate must meet its quality requirements before further processing. Even if two or more batches of intermediates will be blended prior to the next step, they must each meet their respective quality requirements.

Blending is a process somewhat unique to the manufacture of APIs. It is an accepted practice to blend batches of the final API, as long as each of the individual batches meets the predetermined specifications prior to the blending. After the blending is complete, there must be a final test to ensure that the final blended lot is acceptable as well.

A sample of the final lot, blended or otherwise, should be taken and stored for future stability testing, if necessary.

Campaign manufacturing is common in pharmaceutical operations. If successive batches are being made of the same API, it is acceptable for residual materials to be carried from one batch into another, as long as there is adequate control. Adequate control will need to be determined for each API produced, but minimally there must be assurance that degradants, microbial contaminants, or other sources of contamination are not carried from one batch to another.

All operations must be conducted in such a manner that contamination is minimized. This is especially true after the purification steps in the manufacturing process.

In addition to preventing contamination of the API, the safety of the operators must be addressed as well. If the materials may be injurious to the operators and/or the environment, how best to ensure there is no harm to either must be addressed as part of the development of the manufacturing process. It may be necessary, in some cases, for the process to be carried out using dedicated equipment or in dedicated and controlled environments.

A. Compliance Requirements

Clearly, this section requires a large volume of documentation, with the focus being proof that each batch has been produced according to the original design. Each batch is individually monitored, and its manufacturing history is recorded in a production batch record. In-process controls should be evaluated after adequate experience is gained in full-scale production. Test limits must be changed, that is, tightened, if justified by historical results. The quality unit must review and approve all changes to production records, control procedures, and test procedures and/or limits. Any deviation from established procedures, whether planned or not, must be investigated for causes and documented for corrective action.

XIX. ICH Q7 SECTION 9: “PACKAGING AND IDENTIFICATION LABELING OF APIs AND INTERMEDIATES”

This section has four subsections, which state quite specific yet reasonable requirements for packaging materials, labeling issuance and control, and packaging and labeling operations of APIs. They are remarkable in their similarity to the requirements for drug products. They require tight control over the receipt, testing, release, storage, and use of containers and labels. Particular care must be taken to avoid mix-ups of labels, and separate storage areas should be provided for all different labels. Further, access to the area should be restricted to only certain authorized personnel. The labeling operations require the same assurance that the labeling facilities are separate from other activity and that they are adequately cleaned prior to use. All preparatory work must be documented in written procedures. Packaging and labeling operations should be recorded in the manufacturing batch record for each lot of API.

The label must bear the usual descriptive information about the product and include its distinct lot number. For intermediate or APIs with an expiry date, the date must be indicated on the label and on the CoA. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or CoA. Naturally, an effective system must be in place to ensure no materials beyond their expiry period are used and all those requiring retesting are completed before use beyond the controlled time period.

As in other areas of API manufacture, contact surfaces must not be reactive, absorptive, and so forth with the API so as to alter its quality.

A. Compliance Requirements

Well-documented systems must be in place to handle the receipt, testing, release, and use of containers and labels, similar to those control procedures used for raw materials. Packaging and labeling operations must be conducted in separate areas to avoid contamination and mix-ups with other ongoing activity. Inventory management of labels must be practiced, with accountability of all used and remaining labels kept up to date for each lot of labels. Expiry dates or retest dates must be based on analytical evidence obtained under the intended storage conditions, and each specific date for each lot must appear of all labels used to package each lot.

XX. ICH Q7 SECTION 10: "STORAGE AND DISTRIBUTION"

This brief section contains only two parts. It directs that the warehousing procedures and distribution procedures be written and, of course, be consistent with the intended storage conditions for which stability data exist for the material. Materials should be held in a quarantine condition until released by the quality unit. This status control may be a physical separation with appropriate labels or, ideally, through the use of electronic control systems. The distribution history of each lot must be maintained for traceability in the event a recall is necessary.

A. Compliance Requirements

Have written procedures to describe the handling of the materials. Ensure that a tight system is used to prevent use of materials before release by the quality unit. Material should be distributed on a first-in-first-out (FIFO) basis.

XXI. ICH Q7 SECTION 11: "LABORATORY CONTROLS"

This is described in greater detail in the section "Part III. The Quality Control and Quality Assurance Department" of this chapter.

XXII. ICH Q7 SECTION 12: "VALIDATION"

This is the most important section of the cGMPs. As such, it warrants its own chapter in this book. Here are described the essential compliance aspects of validation.

Within the ICH guide, validation is further divided into the areas of its disciplines:

- Validation policy
- Validation documentation
- Qualification [installation qualification/operational qualification (IQ/OQ)]
- Process validation
- Periodic review of validated systems (revalidation)
- Cleaning validation
- Validation of analytical methods

The validation policy is a high-level document stating the approach a firm will use toward validation. The validation approach requires the development scientists and plant management to identify the critical parameters/attributes during the development stage and use that knowledge in the validation of the process.

For each validation activity there is a validation protocol (a study design) written and approved in advance of the execution of validation work. The quality unit must review and approve the protocol, as should other affected departments. The protocol lists the tests to be conducted, along with the acceptance criteria; the tests are chosen to demonstrate the process is in a state of control.

Once the validation protocol is executed, the results of the tests are written into a formal report. Any deviations from the acceptance criteria must be addressed in the report, along with a conclusion about the impact on the consistency and reliability of the process.

Validation is a life-cycle process, which has its roots in the development area.

- Design qualification: verification that the proposed design is suitable for intended use
- IQ: verification that installation complies with the approved design, manufacturer's recommendations, and/or user requirements
- OQ: verification that the equipment performs, as intended, throughout anticipated operating ranges
- Performance qualification: verification that the equipment and/or process can perform according to preapproved specification consistently

Just as there are phases in the validation life cycle, there are three distinct approaches a firm can take toward the validation process.

1. Prospective validation is the preferred approach and is the most common. If other approaches are used, the firm should have a documented rationale as to why it did not use a prospective validation approach. A prospective validation is a formal study that serves to prove the process will reliably yield an API to meet its predetermined quality attributes and all steps along the way are reliable in terms of quality and yield. Validation can best be defined as proof of knowledge of control. For new products, or changes to

processes requiring a process validation, the number of runs must be commensurate with the complexity of the process or the nature of the change under review. Three consecutive successful production batches are typically required; exceptions should be documented. Process validation must confirm the impurity profile of the API.

2. Concurrent validation can be used where a small number of API batches are made on an annual basis. Typically there are three validation batches manufactured in a study, and all three are held pending the results. In the case where the time period between the production of the first batch and third batch is extremely long, concurrent validation can be used. In this case, the first batch is released on its own merit; however, the process is not considered validated. Only when the full protocol requirements are met, in terms of both acceptance criteria and the number of batches, is the process considered validated. The use of concurrent validation is rare and suitable only under special circumstances.
3. Retrospective validation is also rare and must be used judiciously. This approach involves reviewing a large number of batches already produced at the plant so as to affirm the robustness and repeatability of a process. There are very specific assumptions that must be met before retrospective validation can even be considered. There must not have been any changes made to the process during the review period. The process must be a well-understood and characterized process with defined in-process tests and controls. There must not be any significant process failures or deviations during the period. The impurity profile for the product must be well established. Even when all these conditions are met, the decision to use retrospective validation must be a last resort and the justification well documented with approval from the quality unit.

Whatever approach is used for the validation, the goal is to gain the proof of knowledge of control of a process. A study plan, called a protocol, is prepared describing the important parameters that need to be controlled in order to ensure the API will meet its quality parameters and expected yields. To determine those important parameters, data, results, and reports from the research department are used. During the initial development of the process, the controlling parameters should have been discovered, including effective working ranges and targets for charge of components, raw materials, and operating conditions of time, temperature, pressure, mixing rate, and so on. Analytical methods used to evaluate each chemical and physical attribute are themselves first validated. This way, the data generated in the validation are known to be true and accurate.

The protocol defines how the study will be done (the process, equipment, critical steps, and parameters) and who is responsible for its design, execution, analysis, and approval. The sampling activity is also well defined, describing the locations to be sampled, the sampling devices to be used, the quantities required, and time point during processing when they should be taken. The protocol defines all the important process parameters to be studied and analyzed in order to demonstrate each significant step performs reliably in terms of quality and yield. The final approval is reserved for the quality function.

A successful validation study will demonstrate a reliable and robust process. To be able to reach a strong conclusion, there must be an adequate number of batches and tests to statistically demonstrate reliability and robustness.

As part of the life-cycle approach to validation, periodic evaluations of the processes and products will determine the periodicity of revalidation. Certain processes will require an annual revalidation. Revalidation also occurs when there are significant changes to a process or piece of equipment, which would "void" the original validation.

A. Cleaning Validation

After manufacturing is completed, the equipment should be cleaned and made ready for the next process. There needs to be a formal study, executed against a protocol, which demonstrates that the cleaning process used is effective to clean the equipment to a predetermined level of cleanliness. Cleaning validation is part of ensuring contamination and cross contamination are prevented. The protocol must include a description of the equipment to be cleaned, the materials for cleaning to be used, and the cleaning process. The sampling equipment, locations, and procedures must be defined. In addition to visual cleanliness, where analytical methods are used, these methods must be validated to appropriate levels of detection. The limits of detection must be based on sound scientific reasoning. Cleaning is performed to remove not only chemical contaminants but microbiological contaminants as well. The removal of microbes and endotoxins must be addressed in the protocol, where appropriate.

The cleaning process must also be included when there is an evaluation as to the necessity of revalidations.

Analytical methods must also be validated. The approach used for method validation is consistent with the validation of analytical methods for drug products. See the USP monograph on analytical validation procedures.

B. Compliance Requirements

Ensure the critical steps and intermediate quality attributes are defined and based on a scientific rationale, usually from original research information. The person making those decisions must be identified in the protocol. Once the protocol is approved, it cannot be changed during the course of the study. While the documentation of validation studies is a regulatory requirement, it serves the business aspects perfectly because it captures the intellectual property of the firm. The protocol should include ranges for operating parameters. These should come from research information. They need not be tested or challenged during the validation study in full-scale equipment.

XXIII. ICH Q7 SECTION 13: "CHANGE CONTROL"

Having established a validated process, efforts must be implemented to ensure it stays in the validated state. Systems need to be implemented to evaluate both planned and unplanned changes to the process. This refers to any change in materials, conditions, equipment used, and site of manufacture, scale, and so forth. All planned changes must be described and evaluated before being implemented. All concerned departments are involved in this analysis; the final review and approval is required of the quality unit.

Factors to be considered in evaluating the change should include any reasonable aspect of the API or its intermediates that may be affected. This must include attributes that are not routinely tested, such as polymorphism, the emergence of new impurities, and the need for additional stability studies, for example. For this reason, chemical experts familiar with the science must be consulted.

Finally, an analysis of the impact of the change on any filed regulatory documents is necessary, as well as informing the pharmaceutical users of the API. Pharmaceutical manufacturers might have additional quality and performance criteria, which are unknown to the API manufacturer, and these criteria need to be assessed relative to the process change under review.

The group of experts who designed the change then evaluates the completely analyzed and studied process change. The final review and approval is again required of the quality unit.

A. Compliance Requirements

An effective communications system needs to be in place to ensure that the quality unit is informed and involved in planned changes. Unplanned changes are to be discovered through the periodic review of production records (see ICH Q7 section 13). Changes may be classified to their expected degree of impact, and studies can be modified accordingly. Scientific judgment must always be used in evaluating the changes. Systems must be in place to ensure that material under change review is not used for further processing until approved by the quality unit. The decisions about what to evaluate must be documented, as well as why no additional studies are deemed necessary (for example, why polymorphism will not be affected by the change).

XXIV. ICH Q7 SECTION 14: "REJECTION AND REUSE OF MATERIALS"

This section describes the requirements for rejection of materials, reprocessing and reworking, recovery and recycling of solvents in the process, and customer returns of materials.

If specifications are not met and/or if the material is not manufactured in accordance with cGMPs, these materials must be set aside and quarantined until disposition. The disposition can be rejection, reworking, or reprocessing the material. Material is used here to denote incoming materials, intermediates, and/or finished product (APIs). If reworking or reprocessing is determined to be in accordance with regulatory controls, the actual reworking or reprocessing must be conducted and recorded in a manner identical to that of the original manufacturing steps.

The manufacturing of APIs can be distinguished from finished pharmaceuticals in that reprocessing is a far more accepted practice for APIs. "Reprocessing" is defined as the return of an intermediate or an API back into the process and repeating a part of the manufacturing step. Types of reprocessing include either physical reprocessing for example, the repetition of a drying step, or chemical reprocessing. However, if reprocessing is used routinely for any given step, at some point it becomes the normal process. At that point the reprocessing step(s) should be incorporated into the manufacturing process and batch documentation, not as a reprocessing step, but rather as a routine part of the process.

Reprocessing by chemical means involves the repeating of a chemical reaction. This is rarely appropriate, since in repeating a chemical step, new impurities could be produced. A batch requiring chemical reprocessing should first be considered for destruction before salvaging through reprocessing occurs.

Reprocessing by physical means involves the repetition of a step such as a recrystallization or remilling already routinely performed in the validated process. If the routine process does not include such a step, then it is not reprocessing but rather reworking. The actions to be taken in a reprocessing must be documented with a documented rationale for the reprocessing. Reprocessed materials must be evaluated to determine if additional testing is warranted.

"Reworking" is distinguished from reprocessing in that the former is the use of a new step, or steps, *not* part of the routine process. While reprocessing does not require a new and separate process validation, reworking must have its own validation. Reworking requires the approval of the quality assurance unit. Reworking often requires a notification to the governing regulatory authorities and typically requires their approval of the change before putting it into use.

Recovery and recycling of reactants, intermediates, or APIs, in order to be used again, is considered acceptable. However, the use of these materials must be done using validated and documented procedures. If a recovered solvent is to be used in a different process (e.g., to produce a different API), there must be adequate validation and documentation to ensure that it can be used without concern of cross contamination. Recovered solvents must meet predetermined specifications. Where recovered or recycled solvents are used in the manufacturing process, their use must be documented.

When customer returns are received, the material must be placed in quarantine to separate them from approved materials. The reason for the return, as well as investigation into the cause for this reason, must be conducted and documented. The material must be evaluated to determine if the quality of material is affected and/or if the material can be returned to stock. Additional testing may be necessary in order to make that determination. Any testing must be documented. If reprocessing or rework is necessary, it must be performed in accordance with the requirements detailed above.

Where materials have been exposed to extraordinary conditions such as extreme temperatures, smoke from a fire, radiation from natural disaster, or other similar incidents, that material should be destroyed. Testing should be designed to be appropriate for the use of the material.

A. Compliance Requirements

All reprocessing and reworking must come to the attention of the quality unit for final review and approval. Continuous reprocessing to bring a batch into conformance should not be allowed, as it indicates there is something unusual and unknown about the process and/or the quality of the product. The need for additional or new tests must be decided before a reprocessed batch can be released. The quality profiles of reprocessed or reworked batches should be compared to normal, first-time-right, batches. This should include purity and impurity profiles, as well as physical profiles. In general, all rework processes require prior regulatory approval.

For each customer return, document the investigation into the reason and cause for the return. Identify corrective actions where appropriate. The person responsible for quality should make the decision to return material to stock, further process it, or discard it. While this is not spelled out in the regulations, it should be clear that only the quality unit has the authority to return materials to production, as this serves as a release function.

XXV. ICH Q7 SECTION 15: "COMPLAINTS AND RECALLS"

Customer complaints represent a unique opportunity for quality improvement. Complaints can come into a company in a variety of ways: person to person, a telephone call, e-mail, or regular mail. All quality-related complaints received by any employee of the firm must be channeled to the quality department and investigated, and this investigation must be documented. The record must minimally contain the name and address of the person initiating the complaint, the date the complaint was received, and a description of the complaint. The investigation must include the final decision regarding the material, and a copy of the response must be sent to the complainant. Complaints should be periodically reviewed for trends suggesting areas of improvement.

If the complaint is of a serious nature, which might justify concern of the material on the market, local regulatory agencies must be contacted within time frames stipulated in the local requirements. In rare occurrences, recall of marketed products may be necessary. Each firm must have in place procedures that define how a recall is to be conducted. The person responsible for the recall must be identified in the procedure.

A. Compliance Requirements

All complaints must be investigated and documented by the quality department. The recall procedure is one procedure that a manufacturer does not want to gain experience in implementing. However, when a firm finds itself in a recall situation, decisions must be made quickly, and a well-defined procedure can facilitate the communication and decision-making processes. The procedure should identify the sources and types of information necessary for the decision, which functions are to be present in an advisory capacity, and the ultimate decision whether to proceed with a recall.

XXVI. ICH Q7 SECTION 16: "CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)"

Today, there is a growing trend of companies choosing to contract their manufacturing operations to countries offering lower costs. As a result, manufacturers must establish robust systems to select and monitor these operations so as to ensure the quality of the materials they produce is appropriate for the intended product. The FDA published statistics show the number foreign contract manufacturers have doubled in the last seven years and the number of FDA inspections has stayed relatively unchanged. Although the FDA plans to continue the increase of foreign inspection, it has made it clear that the primary oversight responsibility lies squarely with the NDA holder.

When another firm manufactures or tests products or materials, the responsibilities identified in this chapter must be defined as falling under the contract giver or the contract acceptor. A formal document typically captures the assignment of these responsibilities and is termed the quality agreement. Each contract manufacturing or testing situation is unique and will require a quality agreement specifically tailored for that situation.

A. Compliance Requirements

The contract giver and the contract acceptor usually have their own templates for their quality agreements. Thus when a contract-manufacturing situation is entered into, the assignment of responsibilities and capturing these into a quality agreement requires negotiation for not only the responsibilities but also the formatting of the agreement itself. There is no right way except to ensure that there is clarity from both parties as to the responsibilities.

XXVII. ICH Q7 SECTION 19: "APIs FOR USE IN CLINICAL TRIALS"

This section addresses new chemical entities never before used in clinical trials. This section does *not* apply to new clinical trial studies of APIs that are already well defined, perhaps even already approved by regulatory authorities.

This section is a very good example of the wisdom applied and value derived from the joint efforts of the government and industry from the United States, numerous European countries, and Japan. The section is based on a scientific and logical approach to ensuring API quality during the developmental stages of new drug discovery. The guidance provides a good balance between controls and variables as knowledge is gained during the development process. In essence, the guidance provided tells us we should have suitable processes and controls documented to the degree necessary so that we can reproduce the result.

Process controls should be consistent with the stage of development, and tests can be flexible to provide for changes as knowledge of the process develops. Equipment should be calibrated, clean, and suitable for the stage of development. The facilities, including simple chemistry laboratories, for initial batches need to be "suitable" for the developmental stage of the process. The "suitability" criteria, although not defined outright in the section, can logically be concluded as those necessary to ensure the process can be repeated, if necessary.

There should be an independent quality group that releases each batch of API for clinical studies. Tests to evaluate the suitability of raw materials can be rather straightforward at this point; suppliers' protocols may be used, especially if the materials are considered toxic or hazardous. In some cases, the raw materials do not even need to be tested; a simple use test in the manufacturing process will suffice.

The section addresses process variability; it is understood that yields will fluctuate, yet variable yields need not be investigated. The process should not be validated (as described above in ICH Q7 section 12) at this point; more so, the requirements of good documentation should be in place so that the researcher can repeat the work later, if deemed of interest.

For a good understanding of how the various requirements and controls change as the development process advances from API for GLP studies on to clinical studies, see Tables 1 and 2.

Finally, although not discussed in this section, it should be noted that during the API development stage the researcher should be learning, and recording, which variables are critical for process control. That knowledge is necessary in order to prepare a process validation protocol once the API is nearing the commercial stage.

TABLE 1 Examples of Possible API Controls During GLP Studies

Intended use—API for GLP studies

Process	Control
Facility	■ Work area designed to prevent cross contamination
Documentation	■ Written, standardized procedures for good scientific documentation in notebooks or batch records ■ Recorded to a level of detail for process repeatability, signed dated by scientist and witness; include synthetic approaches and procedures documented; and recorded to a level of detail for experiment repeatability ■ Controls in place for general documentation, document management, archiving, and documentation of training
Equipment	■ Calibrated, clean, suitable for use, and adequate to prevent cross-contamination
Personnel	■ Must have education, training, and experience to support assigned functions. ■ Must document and maintain qualification evidence
Starting materials and synthetic intermediates	■ CoA or equivalent
Tracking, storage, and dispensing	■ Material stored under controlled conditions ■ Dispensing history maintained

Laboratory controls

Process	Control
Identification test	■ Specific for compound of interest
Assay	■ 97–103 area % API ○ Precision: determine from three sample preparations ○ Specificity: show resolution of drug substance from most likely and available impurities; recommended use of LCMS ○ Linearity: determine from impurity linearity, if appropriate, or three levels 80%–120% of the concentration specified in the method ■ Chiral assay, if applicable
Organic impurities	■ Resolved from API (by chromatogram) ■ Quantified by area % ■ No more than 3% total impurities and no one impurity >1% by area in HPLC ■ Reporting limit: target reporting limit at 0.05 area%
Inorganic impurities	■ Determined by ROI
Residual solvents (volatiles)	■ Developed specific methods to quantify process solvents ■ Known total residual solvent amount ■ Minimum TGA ■ Reported water content
Physicochemical properties	■ No specific requirements ■ Reported particle size distribution, crystal properties (as applicable) ■ Confirmed polymorphic form ID by XRPD
Stability	■ Addressing the conditions and duration of use for GLP study; may be performed concomitantly with GLP study ■ Room temperature ■ One month minimum accelerated ■ Degradation products detected; identity not required

TABLE 1 (*Continued*)

Laboratory controls	
Process	Control
Reserve samples	■ All studies requiring reserve samples
API release	■ Quality unit (independent from production) accepting or rejecting material ■ Process and analytical documentation review ■ CoA generated by testing lab ■ Batch documentation provided by the manufacturer ■ Packaging release by quality unit ■ Quality providing documentation for approved release

Abbreviations: API, active pharmaceutical ingredient; LCMS, liquid chromatography mass spectroscopy; GLP, Good Laboratory Practice; CoA, certificate of analysis; ROI, residue on ignition; TGA, thermal gravimetric analysis; XPRD, X-ray powder diffraction.

TABLE 2 Controls for API Used in Phase I Clinical Trials

Intended use—API for phase I drug product	
Process	Control
General	■ Must meet ICH Q7: 19.1 Controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API.
Quality	■ Must meet ICH Q7A 19.2 Appropriate GMP concepts should be applied in production with suitable mechanism of approval for each batch. Independent quality unit should be established. Quality, process, and labeling controls should be in place.
Equipment and facilities	■ Must meet ICH Q7: 19.3 Procedures to ensure equipment is adequate should be in place. At minimum the equipment should be calibrated, clean, and suitable for intended use.
Documentation	■ Must meet ICH Q7: 19.9 A system should be in place to ensure that information gained during development and manufacture is documented and available. Records and documents should be retained and controlled. Information used to support release should be appropriately documented (e.g., development and implementation of analytical methods).
Personnel	■ Must have education, training, and experience to support assigned functions.
Control of raw materials	■ Must meet ICH Q7: 19.4 Raw materials should be evaluated by testing and have documented analysis.
Production	■ Must meet ICH Q7: 19.5 Production should be documented. Documentation should include information on the use of materials, equipment, processing, and scientific observations.
Validation	■ Must meet ICH Q7: 19.6 Process validation for the production of APIs for use in clinical trials is normally inappropriate where a single batch is produced. The combination of controls, calibration, and equipment qualification should ensure quality. If batches are produced for commercial use, process validation must be conducted.

(*Continued*)

TABLE 2 Controls for API Used in Phase I Clinical Trials (*Continued*)

	Intended use—API for phase I drug product
Process	Control
Changes	■ Must meet ICH Q7: 19.7 Changes should be adequately recorded.
Reserve samples	■ All studies require reserve samples.
Tracking, storage, and dispensing	■ Material is stored under controlled conditions. ■ Dispensing history is maintained.
Laboratory controls	■ Must meet ICH Q7: 19.8 Analytical methods should be scientifically sound. Reserve samples should be taken and retained. Expiry and retest dating should be established.
Identification test	■ Specific for compound of interest.
Assay	■ 97–103 weight % API ○ Precision: determine from three sample preparations ○ Specificity: show resolution of drug substance from most likely impurities; recommended use of LCMS ○ Linearity: determine from impurity linearity if appropriate or three levels 80%–120% of the concentration specified in the method Chiral assay, if applicable
Organic impurities	■ Adequately separated from API on chromatogram ■ Quantified by area% ■ No more than 3% total impurities and no one impurity >1% by area in HPLC Reporting limit: target reporting limit at 0.05 area%
Inorganic impurities	Determined by ROI
Residual solvents (volatiles)	■ Known total residual solvent amount ■ Minimum TGA. Quantify further if additional undesirable solvents identified ■ Reported water content
Physicochemical properties	■ No specification ■ Reported particle size distribution, crystal properties (as applicable) ■ Confirmed polymorphic form ID by XRPD
Stability	■ Established stability appropriate for length of study ■ Must have supporting stability indicating method (stress testing) ■ One month minimum accelerated preferable ■ Degradation products and process impurities detected
API release	■ Quality unit (independent from production) accepting or rejecting material ■ Material comparable to data from GLP studies (no new or significantly larger impurities) ■ Process and analytical documentation review ■ CoA generated by testing lab ■ Batch documentation provided by group manufacturing the material. ■ Packaging release by quality unit ■ Quality providing documentation for approved release

Abbreviations: API, active pharmaceutical ingredient; GLP, Good Laboratory Practice; ICH, International Conference on Harmonization; CoA, certificate of analysis; ROI, residue on ignition.

XXVIII. PART III. THE QUALITY CONTROL AND QUALITY ASSURANCE DEPARTMENT

The cGMP regulations define the responsibilities of the quality control and quality assurance department throughout all phases of manufacturing. Part III of this chapter on quality reviews the specific laboratory controls and all the quality-related responsibilities throughout the regulations.

A. Laboratory Controls Taken from the FDA's Regulations for cGMP

The first subsection covers general controls. As expected, all activities associated with the testing of materials must be scientifically thought out. Sampling must be based on statistical grounds, and all procedures should be documented. This includes all activities of the laboratory in its efforts to evaluate all materials, from raw materials, to containers, intermediates, in-process controls, and so on to the stability testing of the final APIs.

Testing for the release of final products should be performed on each lot produced. Sampling plans, based on statistical grounds, should also include supportive data illustrating that the batch is homogeneous and the process will always yield a uniform grade of material. The test methods must be validated, which means their accuracy, sensitivity, and linearity over a variety of concentrations of material, specificity, and reproducibility have been established. Such criteria apply to all test methods used throughout the manufacturing process, not only to the API.

Stability testing is also required to demonstrate the material will hold its quality over the labeled storage conditions and time. When establishing the storage conditions for the first time for an API, studies should include the extremes of conditions likely to be seen. The testing protocol should include all and only those attributes that may be affected by the storage conditions. Consideration should also be given to the stability of the product during its planned method of shipment. The regulations offer an adequate amount of flexibility to the storage conditions for the stability study samples. The requirement logically states that the sample container affords the same level of protection as the bulk container. The results from these studies are used to determine either an expiry date or a reevaluation date. Reevaluation dates are preferred, since APIs exceeding their expiry dates are to be discarded, while those with reevaluation dates may be returned to stock following a satisfactory reevaluation.

As APIs are tested for purity, impurity testing on a lot-by-lot basis is also required. The expected impurities should be determined for normal production batches, and new impurities should be hunted down when evaluating a process change.

A sample from each lot of API and key intermediate should be taken and stored for annual visual examination, as well as to cover any future investigative purposes (e.g., to evaluate a customer complaint on the lot).

Finally, if animals are used for testing purposes (although this is rare today), they require the same degree of control and suitability for testing as analytical equipment, reagents, and other aspects of the manufacturing process.

B. Compliance Requirements

Laboratory operations must be documented, and the quality leader must approve any changes. Retesting or resampling is a serious matter that can only be conducted following specific conditions and must be carried out under predescribed written procedures. See the FDA's guidance for industry "Investigating Out of Specification Test Results for Pharmaceutical Production," issued on its Web site (fda.gov), September 4, 1998. An effective calibration program for all equipment and reagents is required. The source of reference standards, their storage, and their use should be clearly defined. All different physical forms of an API must be included in the routine stability study program. Manufacturing change control systems should evaluate all likely attributes that may be affected, as well as additional attributes that are not part of a typical release protocol (e.g., polymorphism or new impurities). Initial lots from a process change should be added to the stability study program. An effective program to visually examine each lot of each key intermediate and API must be established, the results recorded, and any cause for investigation taken also documented.

C. The Quality Unit Responsibilities

1. The Reporting Relationship and General Responsibilities

Throughout the cGMPs reference is made to the quality unit. That is the way the FDA and other agencies address the areas of the organization responsible for quality control, quality assurance, and other QM activities. While the regulations do not mandate to which area or department the quality unit should report, all regulators make it clear they must have a reporting relationship that allows, and encourages, independence of judgment. The people assigned the responsibility to judge the quality of a product; material, or process cannot be expected to do a good job for the company if there is a conflict of interest between them and their direct supervisors. Regulators and company senior management agree on this point because we are dealing with the manufacture of products used to treat human illness and disease. There is no margin for error.

The overall responsibility of the quality unit is to help the organization develop and implement a solid system of procedures and controls to ensure that each batch of API will routinely meet its predefined quality attributes. To execute that responsibility, the quality unit inherits a broad range of authority: to review and approve all procedures, all systems, all changes, all in-process and final product specifications and test methods, all manufacturing procedures, investigations, and so on. The full scope of authority can only be appreciated by a thorough reading of the FDA's cGMP document. Suffice it to say that all activities related to the manufacture of APIs require the approval of the quality unit.

Clearly, top scientists, technicians, and managers are needed in the quality unit in order to facilitate a smooth-running manufacturing organization.

2. Quality Control

The general laboratories of the quality unit are often referred to as the quality control department. This is the area of the quality unit responsible for carrying out the tests on the purchased materials, in-process samples, intermediates, and final APIs and stability studies. In some cases, parts of this testing can be delegated to other departments, such as in-process control tests to the production area. However, the final release decisions are still the responsibility and authority of the quality unit. The quality laboratories are considered part of the manufacturing plant; the quality control function is part of the manufacturing process and comes under the same regulations as production areas. It therefore requires that systems be described in writing, that cGMP training occur on an adequate basis, and so on. The test procedures used in this department must be validated. The equipment used must be qualified to demonstrate its functions as designed, and it must be maintained and calibrated on a sufficiently regular basis to ensure it is always working properly. Any problems that occur must be investigated and corrected.

3. Quality Assurance

This part of the quality unit is responsible for the review and approval of the cGMP written procedures and systems used throughout the site for the manufacturing, control, and release of APIs. The quality department typically has responsibility to write quality policy and standards and to prepare SOPs for the quality control and quality assurance department to follow. The quality unit typically has the responsibility to audit the manufacturing and quality control functions to ensure they are following their procedures correctly and are compliant with other aspects of the regulations, such as performing and documenting investigations, where necessary, and implementing corrective measures, where appropriate.

Another major responsibility of this department is change control management. To effectively evaluate the potential impact of a process change, it is important to contemplate how the predefined quality attributes might be affected, as well as other chemical/physical attributes not normally tested or evaluated. This requires people who have a firm understanding of the chemistry of the process and an appreciation of how a change in the API may affect the drug product process throughout the supply chain.

The significance of the responsibilities of the quality unit and the scope of its influence throughout the manufacturing process, only briefly highlighted in this section, requires that it be staffed with very well-educated, experienced, and skilled people who are good thinkers, communicators, and confident decision makers.

Other duties of this function usually include the handling and investigation of customer complaints, cGMP training, throughout the manufacturing site, and review and approval of major projects, such as validation reports or capital investments, to ensure or improve cGMP compliance.

4. Qualified Persons

In some parts of the world, such as the EU, local regulations require the appointment of a "qualified person" (QP) and in other countries, such as Switzerland and Canada, regulations require the appointment of a "responsible person." Although the terms "qualified person" and "responsible person" are often used interchangeably, there are important legal differences. For the purposes of this discussion the responsibilities of the QP are described.

The European Union Directive 2001/83/EC, requires that a QP, who is named on the manufacturing license, "certify" each batch before release for commercial distribution or clinical supply. The QP is legally responsible to make this certification and is personally liable.

The certification attests that the final batch, and all its ingredients (especially the API), has been manufactured in accordance with GMPs, that is, EudraLex, Vol 4, chapter 1. The QP is typically a licensed pharmacist, biologist, or chemist who has several years experience working in pharmaceutical manufacturing operations and has passed a professional body of examinations, such as the Royal Pharmaceutical Society, which includes assessments by a QP officer and a panel of experienced industry assessors.

To make this certification, the QP must have first-hand knowledge of all manufacturing operations that may impact the quality of the final product, including the manufacturing of the API. Often, a QP will rely on other QPs within the manufacturing chain to make this certification but only after having established strong relationships and effective lines of communication. In most every case, a QP will rely on another QP only if mutual site audits have occurred and found agreeable by both parties.

5. *Analytical Technical Service*

An analytical technical services department should also exist within the quality unit. The functions of this department include helping manufacturing in troubleshooting to determine root causes of quality problems, improving current test methods to make them more efficient or more user friendly, evaluating new technology, evaluating inquiries from official offices such as pharmacopoeia, performing analytical investigations to evaluate complaints against quality, and keeping all current test procedures up to date.

6. *Management of Quality*

The head of the quality function has the overall responsibility for the quality systems at the site or across the company. He or she is not the single responsible person to produce a quality product; that responsibility belongs to the head of manufacturing. This distinction may not always be clearly understood. To delineate the division of responsibility more effectively, the head of quality is responsible for ensuring that the requirements are effectively communicated and understood by plant management and an effective compliance and quality system is developed and implemented to achieve those requirements. It is the responsibility of the head of manufacturing to ensure that the system is properly supported, financed, and strictly adhered to. The head of quality, on the other hand, has the sole responsibility to release the product from the plant for further processing or for sale to a drug product manufacturer. Through the authority to audit, the quality head learns if the systems are being followed; if not, it is his or her responsibility to bring that matter to the attention of the head of manufacturing. If corrective measures are not forthcoming as soon as required, on the basis of the severity of the observation, the quality leader is responsible for adequately communicating the matter to a higher level in the organization regardless of "lines of reporting" as described in organization charts.

A further role of the quality leader is to encourage support and enthusiasm for quality and quality improvement throughout the entire organization. This is best conducted if the quality leader solicits the support and confidence of the manufacturing head, as well as all other technical management at the site, and among senior leadership throughout the organization.

Finally, the quality leader must ensure that his or her staff has access to current information, practices by other companies, and enforcement efforts by the regulatory authorities. This is necessary in order to ensure that the manufacturing system continues to keep pace with the "current" component of the cGMPs.

APPENDIX 1 Typical Attributes Evaluated to Control and Ensure Commercial API Quality

Attribute	How determined	Specification example	Rationale
Description	Visual examination	Agrees with standard or typical product description	This is a traditional organoleptic "test" with very limited value due to its subjectivity; nevertheless, it remains in use, simply to provide the assurance that the batch appears similar to expected.
Identity	IR, NIR, FTIR, NMR, UV, MS etc.	Agrees with standard	These electromechanical/ spectroscopic analyses help verify that the correct chemical bonds and arrangement of functional groups are present and elucidate the structure of the molecule.
Water content	Karl Fischer	Variable, reported as % by weight, compares to normal ranges	The Karl Fischer test determines how much water is present due to inefficient drying and the hygroscopic nature of the molecule and/or is chemically bound as a hydrate but does not distinguish between these types.
Residual solvents	GC	Typically reported as "not more than X %"and, if the solvates controlled/ specified in an official pharmacopoeia, their limits specified	This determines how much residual, or volatile, process solvents adhere to the molecule from inefficient drying and/or as a bound solvate but does not distinguish between the two types.
Crystallinity/ morphology	X-ray diffraction	Conforms to diffractogram of desired polymorph	The output, called a "diffractogram", provides precise mechanical information about the shape of the crystal, reporting three dimensions of the crystal's axis and the arrangement/packing of the molecules within the crystal.
Melting range	Differential scanning calorimetry	Thermogram and melting curve conforming to desired polymorph	The output, called a "thermogram" provides an indication of heat absorption of the molecule during the melting phase; a comparison with a reference standard of the product provides an indication of the sample's purity.
Particle size distribution	Microscopy, laser obscuration, laser light scattering, laser diffraction, etc.	Profile of distribution matching typical results	The output is a distribution of particle sizes, showing the percent present at ever-increasing sizes and a range and mean reported in microns.
Heavy metal content	USP methods	Typically reported as less than X ppm	This indicates the ppm of (potentially toxic) heavy-metal contaminants/impurities in the drug substance.

(*Continued*)

APPENDIX 1 Typical Attributes Evaluated to Control and Ensure Commercial API Quality (*Continued*)

Attribute	How determined	Specification example	Rationale
Palladium (Platinum), etc., content	AA, ICP-OES, ICP-MS	Typically reported as less than X ppm	This indicates the ppm of specifically palladium or platinum (or any specific metal when using the appropriate detector) in the drug substance. This test is conducted if a specific metal was used as a catalyst during the synthesis or to provide a general screen of typical residual metals present from the process.
Chiral purity	HPLC or optical rotation	% Enantiomeric excess, or degrees specific rotation, compared with a chirally pure reference standard	This provides an indication of the enantiomeric purity of a chiral material. This test is conducted when the drug is designed to exist as a single enantiomer or when an enantiomerically pure chiral raw material was used in the synthesis, and the chirality or degree of enantiomeric purity is deliberately destroyed to yield a racemic mixture. In this case the specification would be, for example, less than 2% enantiomeric excess.
Impurity	HPLC	Limits based on process averages, safety, and/or regulatory expectations; generally reported as "total less than X%, no known impurity greater than 0.5%, no unknown impurity greater than 0.1% (or lower—sometimes more detailed)	The impurity profile is very important both as an indicator of the purity as well as a show of consistency and reliability of the manufacturing and purification processes.
Assay	HPLC	Not less than 98%, not more than 102%; compared with reference standard of known purity/ potency (weight/weight basis, on dried samples)	This provides proof that the process yields the expected potency.
Microbial purity	Viable aerobic counts, yeasts and molds, specific indicator organisms	See USP or EP	Microbial tests reveal the bioburden associated with the drug substance. The biomaterials come from, generally, process water used in the final step. The test is not necessary if the final step is nonaqueous, and the drying and subsequent handling is controlled such that bioexposure is limited or not possible.

Abbreviations: NIR, near infrared; IR, infrared; FTIR, fourier transform infrared; UV, ultraviolet; MS, mass spectrometry; GC, gas chromatography; AA, atomic absorption; ICP-OES, inductively coupled plasma-optical emission spectrometer; ICP-MS, inductively coupled plasma-mass spectrometry; ppm, parts per million.

9 Environmental Control

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I. INTRODUCTION

The focus for this chapter is on a basket of environmental issues important to a bulk drug manufacturing facility staying in compliance with its environmental regulations and understanding its expectations from the emerging global framework called sustainability. The first group of issues discussed can be thought of as management tools serving as a type of scaffolding supporting the facility's compliance efforts. The issues associated with management tools are license to operate, management systems, environmental scoping, project schedules, environmental profiles, and environmental dossier. The second group of issues is directly related to environmental compliance and is associated with applicable regulatory requirements, control equipment plans, operational flexibility, and management of change. Finally, the last group of issues addresses the emerging topics of sustainability and green chemistry initiatives within the pharmaceutical industry. The topic treatment is overview in nature but hopefully gives enough to the inexperienced and veteran practitioners for them to utilize the references for more depth and follow-up.

Given the global nature of the pharmaceutical business and the expanding presence of bulk drug manufacturing in countries such as India and China, it is important that every organization have a fundamental understanding of the management tools that support a strong compliance effort at the manufacturing site. In addition to focusing on compliance, every facility is increasingly being called on by stakeholders to address global sustainability issues at the operating plant level. Compliance is a daily must and never gets a time-out while sustainability is a long-term organizational aspiration. High-performing organizations are able to maintain compliance well and execute sustainability projects without trading compliance for sustainability.

The presence of trace pharmaceuticals in drinking water, surface waters, groundwater, and sediments—known by the acronym PIE, which stands for "pharmaceuticals in the environment"—continues to be an issue of great concern to researchers in academic, government, and industrial organizations. However, the PIE issue is not addressed in this chapter because the current thinking by experts points to patient consumption and subsequent human waste excretion from patients and discharge to a public-owned treatment works, as the significant source of active pharmaceutical ingredients (API) and metabolites into the environment (1). Bulk drug manufacturing facilities that are currently regulated by national or regional drug agencies (i.e., U.S. Food and Drug Administration, European Medicines Agency, etc.) are also regulated by national or regional environmental control organizations (i.e., U.S. Environmental Protection Agency, European Union) with existing processes for allocating effluent discharge limits. Should a PIE issue from an individual facility arise, revision of the facility's effluent discharge permit may be part of the remedy implemented to address local concerns. In locations where environmental regulatory oversight is weak or ineffective, one of the first steps toward an acceptable local PIE remedy would be a strengthening of the regulatory and discharge permit process.

Product stewardship is a product-centered approach to environmental protection. The product stewardship framework to solve the PIE challenge is still developing with public policy evaluation, PIE research, and wastewater control technology evaluation. The product stewardship framework recognizes that product manufacturers must take on new responsibilities to reduce the environmental footprint of their products. However, real changes cannot always be achieved by producers acting alone: retailers, consumers, and the existing waste management infrastructure need to work together to help provide the most workable and cost-effective solutions (2). A holistic solution to the PIE challenge awaits.

II. LICENSE TO OPERATE

The strategic framework to view bulk drug manufacturing is known as the license to operate. The license to operate is the collective approval that stakeholders give to a company to locate and pursue its business interest in a local community. It is gained by trust and performance but can also be lost if a company does not have the right programs, policies, and procedures to maintain the right relationship with its stakeholders. While the license to operate may involve some permits from state or regional authorities and some approvals from local authorities at the manufacturing site, it is not a piece of paper or certificate to file away in a desk drawer. Instead, the license to operate is an unwritten contract, some call it a social contract, between the operating facility and the facility's key stakeholders—such as neighbors, local government representatives, students, nongovernment organizations (NGOs), and other interested parties (2,3).

One expert notes that the license to operate is the new way of engaging with key stakeholders who have a rising set of expectations about a company and its local operating sites; those expectations span a broad range of issues such as environmental protection, human rights support, codes of ethics, NGO partnerships, and business plan and strategy consultation (4).

One of the significant hallmarks of the license-to-operate approach is consultation and consensus building with stakeholders before a significant initiation or change at the facility takes place. In fact, the license-to-operate approach is a process that is never turned off but continues over the life cycle of the facility. Because API manufacturing is global in scope, it is also incumbent on the operating facility to ensure that local customs and cultural considerations are designed into the license-to-operate process.

A robust license-to-operate process gives a company a higher probability of securing the start-up of the initial operation and future expansion. A worse case outcome of a weak license-to-operate process results in a facility not starting up or having to shut down after start-up. The more likely outcome of a less than robust license-to-operate process is the case where the facility experiences excessive approval times and excessive amount of meetings before final approval is granted.

A recent incident with Tata Motors (India) is an example of the challenges a company faces in maintaining the license to operate. Tata Motors stopped work at its $350 million car factory in West Bengal State and was forced to draw up alternative production plans in response to planned protest by farmers and local activists over compensation for land used to build the facility; the company reports that it will abandon the factory, built to produce the Nano automobile, and 10,000 associated jobs to a new location in Gujarat State (5,6).

The job of designing and executing a facility's license-to-operate process goes well beyond the job descriptions of the facility's public affairs and environmental managers. The license-to-operate process is one of the facility's highest business priorities, and it is advisable that the entire facility leadership team be appropriately engaged in securing and maintaining the license to operate for the operation's long-term viability. It is critical that the leadership team conduct the necessary training and awareness to the entire facility about the importance of maintaining environmental compliance as the centerpiece of the site's license-to-operate strategy.

III. ENVIRONMENTAL MANAGEMENT SYSTEMS

An environmental management system (EMS) is a business process that guides an organization in achieving its environmental goals and policies. The complexity of the EMS ranges from a few sheets of paper in a three-ring binder to a global network of databases. Regardless of its complexity, the EMS helps an organization to answer five critical questions:

- What is important?
- How do things get done?
- How is progress measured?
- How are issues communicated internally and externally?
- What measures are in place to ensure compliance?

As noted in Figure 1, the EMS process usually follows the classic "plan, do, check, and review" model, which is designed as a cycle of activities beginning with planning or goal setting and terminating with management review. The opportunity to implement an EMS stems from many sources: At least a dozen countries have passed EMS requirements; for example, the United Kingdom has developed BS 7750, the European Union has passed the Eco-Management and

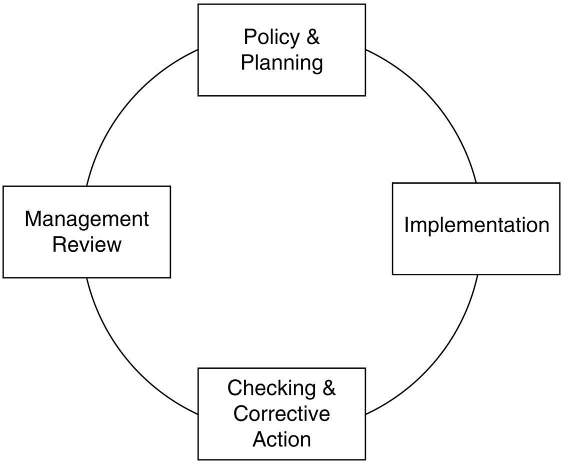

FIGURE 1 The environmental management system (EMS) model follows a continuous cycle of plan, do, check, and review to guide an organization in achieving its environmental policies and goals.

Audit Scheme (EMAS), and the Chemical Industry Association, American Chemistry Council, has developed the Responsible Care© Program (7). One of the EMS programs that appeals to companies operating globally is the ISO 14001 Environmental Management System, developed by the International Standards Organization (ISO). The 18 elements of ISO 14001 are explained briefly in Table 1. Experience from many practitioners and critical reviewers of environmental, health, and safety (EHS) management systems indicates that one of the most significant success enablers is the continued sponsorship and support of senior management at the highest level of the organization (7,8). Another key enabler for ensuring the execution of a successful EMS program is the presence of component environmental leadership at the site and a cadre of subject matter experts either located at the facility or available to the facility via an external network.

IV. ENVIRONMENTAL SCOPING

The topic of environmental scoping arises to meet the business needs driven by a range of requirements, such as (a) a new product introduction, (b) capacity expansion of existing products, (c) new or modified environmental requirements, and (d) process improvements for yield improvements and waste reductions.

For ease of further discussion, any of the business drivers described previously can be considered a "proposed change." The objective of environmental scoping is to gather enough critical information about the "proposed change" to identify the one item that will require the longest time to obtain a new permit or modification to an existing permit. Whether the proposed change is the construction of a new facility (green field) or the modification of an existing facility, the project team will have some individuals who are responsible for developing the environmental scoping document and the initial drafts of the preliminary permit project schedule. It is extremely important for the entire project team to be aware of the permit timing requirements because, in many instances, the time to obtain environmental permits for the "proposed changes" needs to be properly included into the overall construction schedule. In many jurisdictions, certain construction activities may not begin until all the environmental permits are secured.

V. PERMIT PROJECT SCHEDULES

Some permit schedules are quite simple and can be obtained within weeks while other permit schedules are quite complex and may take as long as 18 to 24 months to secure, if not longer. Table 2 is an example of a permit schedule for a "proposed change" involving a new product introduction. The other complicating factor to keep in mind is that the process designed, in some instances, is still in development, so the scoping information continues to change and may in turn change the preliminary permit schedule. The environmental scoping and preliminary permit schedule is a very dynamic phase, and it is important for the resource team members to constantly stay in touch with each other as the preliminary permit schedule can impact the overall project schedule.

At the end of the scoping stage, a final process—or the one that is the basis of the regulatory filing—is the basis for the resources team to complete the necessary

TABLE 1 The 18 Elements of the ISO 14001:2004 EMS Address all the Significant Environmental Issues Required for Effective Program Implementation and Continuous Progress

Element	**Description**
4.1 General	Ensure that organization establishes, documents, implements and continually improves its EMS.
4.2 Environmental policy	Develop a statement of the organization's commitment to the environment.
4.3.1 Environmental aspects and impacts	Identify environmental attributes of products, activities and services and their effects on the environment.
4.3.2 Legal and other requirements	Identify and ensure access to current relevant laws and regulations applicable to the facility's operations.
4.3.3 Objectives and targets, and environmental management program	Set environmental goals for the organization and plan actions to achieve objectives and targets.
4.4.1 Structure and responsibility	Establish roles and responsibilities within the organization
4.4.2 Training, awareness, and competences	Ensure that employees are aware and capable of their environmental responsibilities.
4.4.3 Communication	Develop processes for internal and external communication on environmental management issues.
4.4.4 EMS documentation	Maintain information about EMS and related documents.
4.4.5 Document control	Ensure effective management of procedures and other documents.
4.4.6 Operational control	Identify, plan and manage the organization's operations and activities in line with the policy, objectives, targets and significant aspects.
4.4.7 Emergency preparedness and response	Develop procedures for preventing and responding to potential emergencies.
4.5.1 Monitoring and measuring	Monitor key activities and track performance including periodic compliance evaluations.
4.5.2 Evaluation of compliance	Develop procedures to periodically evaluate compliance with legal and other requirements.
4.5.3 Nonconformance, corrective, and preventive	Identify and correct problems and prevent recurrences.
4.5.4 Records	Keep adequate records of EMS
4.5.5 EMS audit	Periodically verify that the EMS is effective and achieving objectives and targets.
4.6 Management review	Periodic review of EMS performance.

Abbreviation: EMS, environmental management system.

Source: ISO 14001 Environmental Management System Self – Assessment Check List. Global Environmental Management Initiative (GEMI). November 2000 (revised).

TABLE 2 A Typical Schedule for Obtaining an Operating Permit

Task	Month										
	1	2	3	4	5	6	7	8	9	10	11
Preliminary data package submitted for agency review	■										
Pre-application meeting with permitting agency	■										
Pre-application modeling study conducted and submitted		■									
Permit application completed and submitted			■								
Agency review I			■	■							
Additional data submitted based on agency request					■						
Agency review II						■	■				
External technical consultant retained and meets with agency							■				
Agency review III								■			
Draft permit issued for public comment									■		
Facility meets with agency to negotiate final permit terms										■	
Agency issues permit to construct and two years of operation											■
Facility modifies its dossier to include new permit											■

The permit schedule shows that the permit process sometimes has a pre-phase and can have many starts and stops before the regulatory agency issues the authorization to construct and operate the new production process.

permit applications and to determine the expected time to receiving permit approvals. Depending on the jurisdiction and country where the process is being permitted, the permit application may require the facility to list all of the raw materials used in the process and the resulting environmental emissions. Some of those raw materials may be process solvents, cleaning agents, or the starting materials used in the formation of an isolated intermediate or the final bulk drug.

VI. ENVIRONMENTAL PROFILE

The bulk drug environmental profile is that unique set of physical-chemical properties that determines the partitioning, or distribution, of the bulk drug

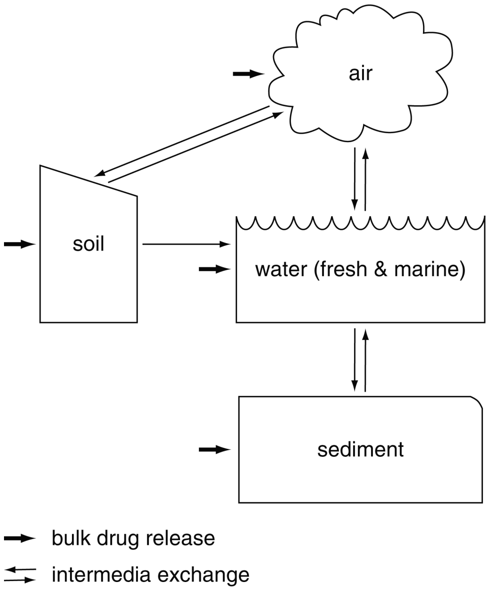

FIGURE 2 The environmental fate and effects of bulk drug substance is determined by environmental testing that determines how much the bulk drug partitions and moves in the various media such as soil, water, air, and sediment. The data from environmental testing forms the basis of the environmental risk assessment that is submitted as part of the drug registration application requesting marketing approval. Schematic of environmental compartments adopted from the level III model. *Source*: From Ref. 9.

substance into various environmental media and the persistence in each media once the bulk drug substance is introduced. The bulk drug environmental profile also includes an indication of the bulk drug's aquatic toxicity or its impact to marine populations. A schematic of a four-component environment of soil, air, water, and sediment is shown in Figure 2 and represents a simple model of the actual environments where a bulk drug might be introduced (9). As Figure 2 notes, the data used to prepare the environmental profile are collected during the bulk drug development process. The environmental profile data are used to prepare the environmental risk assessment that is submitted as part of the drug registration application requesting marketing approval from various regulatory bodies throughout the world (i.e., Food and Drug Administration, European Medicines Agency, Health Canada, etc.). A few of the critical parameters of the environmental bulk drug profile are the following (10–12):

- Water solubility—a maximum percentage, by weight, of the bulk drug that will dissolve in a unit volume of water at a standard temperature and usually expressed in milligrams per liter.
- Octanol-water partition coefficient (K_{ow})—the ratio of the equilibrium concentration of the bulk drug in the octanol phase to the bulk drug in the aqueous phase; the log K_{ow} is the value most often reported in the literature, and a large value of log K_{ow} (greater than 3.5) indicates the need for additional evaluation to determine the extent of the drug's persistence in the environment.
- Lethal concentration 50 (LC_{50})—a standard measure of the aquatic toxicity of the bulk drug that will kill half of the sample population of a specific test organism in a specified period of time; LC_{50} is usually measured in milligrams per liter, and the lower the LC_{50}, the more toxic the bulk drug is to marine populations.

- Biodegradability—the breakdown of the bulk drug by microorganisms (bacteria and fungi) in the natural environment or in a wastewater treatment facility.
- Organic carbon adsorption coefficient (K_{oc})—the ratio between the concentration of bulk drug in the soil or sludge and the concentration of bulk drug in the aqueous phase at adsorption equilibrium; the K_{oc} value is a measure of how tightly the bulk drug binds or sticks to soil/sludge particles; the greater the K_{oc} value, the less likely the bulk drug will leach from the soil or sludge matrix.

While the majority of the data collected for the environmental profile predict the chronic or long-term behavior of the bulk drug in the environment, an acute parameter such as aquatic toxicity is also of critical importance for the day-to-day operations of a manufacturing site since the accidental discharge of bulk drug substance, as any of the following release scenarios can be very problematic for the site:

- spill to site grounds,
- spill to site wastewater treatment facility,
- spill to site processing building or warehouse,
- spill resulting from on-site firefight activities,
- spill to off-site wastewater treatment facility,
- spill to off-site drinking water intake for downstream communities, and
- other spill scenarios not listed.

When a manufacturing site is processing a bulk drug with an extremely low LC_{50}, there is no room for execution error, and the site must ensure that all emergency procedures are clear to staff, that containment structures are empty and operational, and that all alarms and shut-off valves are in proper working order so that the site can respond quickly to contain any process abnormalities.

VII. ENVIRONMENTAL DOSSIER

As more pharmaceutical companies increase the percentage of their processes manufactured by tollers and contract manufacturers, the utility of the environmental dossier increases. The format and the level of details vary from company to company, but the environmental dossier is the complete body of environmental knowledge organized by the process owner for use by internal manufacturing networks or external tollers or contract manufacturers. The environmental dossier is generally a chapter or subset of the technology transfer package prepared by the process owner. An example of a hypothetical environmental dossier is shown in Table 3. The dossier can be maintained in either paper or electronic form—the most critical thing is that the dossier be complete and up to date.

It is critical that the bulk drug owner have a business process in place ensuring that the environmental dossier reflects the most current data and has been reviewed by the appropriate technical and legal teams before the documents are released. In going from the first site of manufacturing to another internal site or to an external contractor, the environmental dossier is not just "tossed over the fence" to another team. The environmental dossier serves as an engagement document that starts a series of questions and answers that the sending and receiving parties complete until there is a good understanding of the data provided and its operational significance.

TABLE 3 Example of EHS Dossier

Section	Subject	Documents
100	Material balance	Solvent waste per kg product
		Aqueous waste per kg product
		Hazardous waste per kg product
		Special waste per kg product
200	Cleaning	Solvent and aqueous waste per campaign
300	Safety and industrial hygiene	Thermal hazards data
		Material safety data sheet, MSDS
		Environmental control limit
		Industrial hygiene methods
		Compound specific analytical testing methods
		Other (case by case determination)
400	Environmental profile	Solubility data / bulk data
		Lethal concentration 50, LC_{50}/48 hour for marine and fresh water environments
		NOEL (no observable effect limit)
		Special handling procedures
		Waste classification sheet
		Octanol-water partition coefficient, K_{ow}
		Organic carbon distribution coefficient, K_{oc}
500	Other environmental data	Fate and effect study summaries
600	Labeling	Global guidance
700	Transportation	Global guidance

The EHS dossier summarizes the safety and environmental body of knowledge that the bulk drug owner uses to communication vital information to internal manufacturing networks and external tollers and contract manufacturers.
Abbreviation: EHS, environmental, industrial hygiene and safety.

VIII. APPLICABLE REGULATORY REQUIREMENTS

The often quoted phrase that the "devil is in the details" is illustrated by the topic of applicable regulatory requirements. With regards to Table 1, the applicable regulatory requirements are covered by element 4.3.2 of the ISO 14000 Environmental Management System. In the most simplistic form, the applicable regulatory requirements are all of the emission limits or work practices that should be a in a facility's operating permits. The more refined and nuanced view of applicable requirements would be a list of every legal requirement that both the operating facility and the regulating authority agree to apply to every aspect of the process that is currently operating at the facility. Good advice to any facility is to have a discussion with the regulatory authorities in advance of operating the process to get agreement of what laws and regulations apply and do not apply to the process in question.

A helpful view of applicable requirements is to think of them as a "layer cake" of compliance limits that apply to the bulk drug manufacturing process. Since there is no single source or document that clearly spells out what applies or does not apply, there is a bit of due diligence, or detective work, that a facility must conduct to ensure that its list of compliance requirements is complete and that the facility has identified all the appropriate "layers of the compliance cake." Given that the organization of government in a country sometimes has at least three levels (i.e., municipal, state or provincial, and national), the task for the facility is to investigate the regulatory agencies at different levels of government to determine what emission limits apply to the facility's operations.

For example, Table 4 shows the air quality standard for the air pollutant known as $PM_{2.5}$ in various places around the world. The milling unit at a bulk drug manufacturing facility may be subject to a $PM_{2.5}$ limit (expressed in units of micrograms per cubic meter). The task for the facility is to determine if a $PM_{2.5}$ limit applies to the milling operation. If a $PM_{2.5}$ limit applies, the next question for the facility is to identify the value of the emission limit. Next, the facility needs to identify what local law or regulation contains the limit—and hence, what level of government is responsible for ensuring compliance to the $PM_{2.5}$ limit. Finally, the

TABLE 4 Example of the Air Quality Standard for Fine Particulate Matter, $PM_{2.5}$

Country/Organization	Standard (micrograms/cubic meter)	Averaging time
Australia*	8	Annual
Canada **	30	24 hour target by 2010
China***	No standard currently exist	_
European Union****	25	Annual
India*****	40	Annual (proposed)
United States******	15	Annual
World Health Organization*******	10	Annual

An example of national air quality standards for fine particulate matter, known as $PM_{2.5}$, which represents particles with diameters less than 2.5 μm. Values vary throughout the world for the $PM_{2.5}$ air quality standard. The emission limit for $PM_{2.5}$ is a value established by local regulatory agencies to ensure that the local area is able to meet and maintain the national air quality standard. The emission limit, not the air quality standard, is the value that the facility has to meet in its operating permit.

Source: * http://www.environment.gov.au/atmosphere/air quality/standards.html (accessed Nov 2008)
** http://www.env.gov.bc.ca/air/airquality/pdfs/aqotable.pdf (accessed Jan 2009)
*** He K, Yang F, Ma Y (et al.). The characteristic of $PM_{2.5}$ in Beijing, China. Atmospheric Environment Oct 2001 35(29): 4959–4970
**** http://www.europa-eu-un.org/articles/en/articles_7826_en.htm (accessed Jan 2009)
***** http://wwww.baq2008.org/system/files/sw26_Sengupta+presentation.pdf (accessed Jan 2009)
****** http://www.epa.gov/air/criteria,html (accessed Nov 2008)
******* http://www,int/mediacentre/factsheet/fs313/index.html (accessed Jan 2009)

facility needs to determine how it will demonstrate and document compliance to the $PM_{2.5}$ limit that meets both record-keeping and agency inspection requirements.

Three other useful things to look for when investigating applicable requirements for bulk drug processes are the topics of exemptions, triggers, and de minimis limits. As the word suggest, exemption is that section of the law or regulations that completely excludes a facility, a portion of a facility, a process, or a portion of a process from the law or regulations. A facility investigator should review the regulation or the appropriate portion of the regulation before concluding that any portion is exempt from certain requirements. Triggers are expressions of the various criteria used to determine that the bulk drug process is subject to a particular applicable requirement. The following is a small sampling of how triggers are sometimes expressed in the regulations:

- a mass limit, such as any chemical process producing more than 1000 metric tons of isolated final products intended for medicinal use in humans,
- a concentration limit, such as any wastewater containing organics in concentrations greater than 5000 mg/L coming from a pharmaceutical production process,
- a concentration and chemical limit, such as any distillate streams from a pharmaceutical production process containing methanol in concentrations greater than 10,000 ppm,
- a chemical on a list, such as "a covered process means any chemical manufacturing process containing any of the chemicals listed in Appendix One of the Final Pharmaceutical Effluent Guidelines," and
- a process located at a facility listed by a particular industrial code or classification, such as chemical production processes in the Standard Industrial Classification 2833.

Finally, the de minimis designation is sometimes mentioned as an explicit limit within the regulations for a particular chemical or activity. The word de minimis is Latin in origin and means "of minimum importance" or "trifling." For example, an air toxic regulation may state something like "the release of chloroform into the atmosphere is prohibited except in de minimis quantities per hour." In this example, the regulations may further explain that de minimis means less than or equal to 1/10 of a pound or about 45 g/hr. In the cases where de minimis is not defined within the regulations, a facility representative may need to meet in person with the regulatory agency to negotiate a case-by-case limit supported by the de minimis language in the regulation.

Once the operating facility has completed its due diligence activities, all the identified applicable requirements are summarized into an operating permit that gives the facility the legal authorization to manufacture a number of bulk drug products. The operating permit identifies which laws and regulations apply to the facility's processes and how the facility demonstrates compliance with the identified requirements.

IX. CONTROL EQUIPMENT PLAN

The environmental control equipment used at a bulk drug facility includes, but is not limited to, the following types of equipment:

- Shell and tube heat exchangers for organic vapor streams
- Packed bed scrubbers for acid gas and particulate streams

- Thermo-oxidizers for organic vapor streams
- Venture scrubbers for acid gases and particulate streams
- Rotary kiln incinerators for organic vapors and solid waste
- Carbon absorbers for organic vapor or liquid streams
- Neutralization tank systems for aqueous streams
- Conservation vents for organic liquid storage tanks
- Cyclones and bag houses for particulate streams
- Nitrogen blanketing for liquids in process vessels or small storage tanks

Environmental control equipment is at the center of the protection that a facility provides to the people, communities, and ecosystems surrounding the facility. Thus, the facility leadership needs to pay special attention to all of the control devices installed and operating at the facility. The control equipment plan is a key management tool that should be reviewed and revised periodically with operating staff and facility leadership. The control equipment plan contains the sections devoted to awareness, preventative maintenance, and performance evaluation.

Awareness is the first component of the plan. Environmental control equipment is installed to reduce the emissions from the various unit operations (i.e., storage tanks, feed tanks, reactors, dryers, etc.) to ensure compliance to the regulatory standards for the equipment trains producing bulk drug products. A database of control equipment is the starting point for awareness. Among other things, the database contains the physical location of the equipment, the installation date, the individual pollutants controlled, the control limits consistent with the facility's operating permits, and the control parameters generated by the equipment. Another important aspect of awareness is communication to the operating areas about who is responsible for ensuring that the equipment is in place, is operating properly, and is providing the documentation to ensure continued compliance. Process-specific training, appropriate signage, and daily operating instructions are a few of the avenues that a facility can use to communicate the importance of environmental control equipment in maintaining compliance to the facility's operating permits.

The need for scheduled preventative maintenance is the second requirement of the plan. Either by operating permit requirement or by recommendation of the control equipment vendor, each piece of control equipment should have a scheduled maintenance that is documented by paper or electronic record. Scheduled preventative maintenance increases the likelihood that the control equipment is 100% reliable while the bulk drug processing is taking place. Some operating permits may have conditions where a piece of control equipment is interlocked to the process equipment so that, if the control equipment is not functioning within acceptable ranges, the process equipment cannot operate. Depending on the permit limits that the control equipment is expected to meet and the type of chemical being controlled (i.e., acid gas, particulate, toxic gas, etc.), the performance of the control device may be compromised due to a lack of scheduled maintenance. The classic example of a control device compromise is the case where 2 to 3 ft of packing height is lost in a packed bed scrubber due to the settling of packing material over time; upon visual inspection by the regulatory agency, the facility is facing a non-compliance situation since the operating permit required a specified height of packing as a permit condition.

Performance evaluation is the last component of the control equipment plan. At some periodic frequency, a subject matter expert or team of subject matter experts conducts an evaluation of the deviations from the facility's control devices. It is important that a robust root cause analysis is conducted on all of the deviations to ensure that the causes leading to deviations are recorded in the appropriate categories, such as human error, procedural error, or equipment failure, that may require further subdivision to identify the single event or combination of single events responsible for the deviation.

The development and use of the problem-solving and quality improvement process known as six sigma is a powerful set of tools that a facility can use when evaluating control device performance. One expert describes six sigma as a business improvement approach that seeks to find and eliminate causes of mistakes or defects in business processes by focusing on outputs that are of critical importance to customers (13). Another observer believes that the average American company operates at a four sigma level—which is the equivalent of a 0.6% defect rate or 6210 defects per million opportunities, while six sigma performance is a defect rate of 0.00034% or 3.4 defects per million opportunities (14). The complexity of many control device systems may require the disciplined six sigma improvement methodology known as DMAIC: The DMAIC framework is a process consisting of the five phases: define, measure, analyze, improve, and control (15). In the context of the control device evaluations, the reviewing member or team is looking for every deviation from the desired control setting and every deviation that ultimately resulted in a noncompliance event. The DMAIC process determines the baseline sigma performance of the control devices and a plan to improve the sigma performance on an ongoing basis.

Given that the number of permit control parameters and the monitoring frequency for each control device is different, the annual opportunities (control parameter measurements) may vary significantly from one control device to another. For example, a shell and tube heat exchanger used to control organic vapors from a single process reactor might have the following control conditions: two control parameters of coolant flow and exit gas temperature measured and recorded once per hour for a maximum operating time of 8760 hours per year. Operating 24 hours per day and 329 days per year (90% equipment availability), the shell and tube heat exchanger's six sigma performance equates to 1 compliance deviation every 19 years! For the shell and tube example operating at 90% availability, the number of annual opportunities (measurements) is 15,768.

Looking at another example, a thermo-oxidizer controlling the vent gases from a train of process reactors connected to a continuous emissions monitor might have the following control conditions: 8 control parameters (inlet and outlet oxidizer temperature, inlet and outlet gas flow, inlet and outlet organic concentration, residence time, and acid gas concentration) measured and recorded every 5 seconds for a maximum operating time of 8760 hours per year. For the thermo-oxidizer example operating 24 hours per day and 347 days per year (95% equipment availability), the six sigma control performance is equivalent to 2 compliance deviations per year. The number of opportunities (measurements) for the thermo-oxidizer example is 798,912 per year!

The goal of the performance evaluation is to ensure that the design and operation of the facility's environmental control equipment is capable of eliminating noncompliance deviations at the facility. Once the current and six sigma performance levels are identified for each piece of control equipment, the facility can evaluate the various improvement options, identified from the six sigma DMAIC process, to sustain compliance.

X. OPERATIONAL FLEXIBILITY

Operational flexibility is best understood by first defining the concept of the "operating envelop." The operating envelop is simply the intersection of three sets of requirements: the process steps from a specified bulk drug process, a specified equipment train with its associated pieces of individual equipment, and the specific regulatory expectations identified by the applicable requirements from the jurisdiction where the process is permitted. Figure 3 shows a graphical representation of the "operating envelop" for a generalized bulk drug process. As a hypothetical example, Figure 3 can also be described as "steps one to five of product XYZ operating in equipment train 500, consisting of 26 pieces of equipment designated by the letters A to Z, subject to the general requirements of chemical manufacturing, the discharge of pharmaceutical wastewater to regional treatment works, and the generation of hazardous waste and non-hazardous waste from an authorized pharmaceutical process."

Given that the operating envelop is a unique set of constrains linking regulatory requirements to specific pieces of processing equipment, operational flexibility relates to the speed with which the operating facility can make regulatory permit changes to accommodate new products and modification for existing products. A flexible operating envelop denotes a great amount of operational flexibility granted by the permitting authority, and permit changes are executed expeditiously. On the other hand, a stiff operating envelop denotes less operational flexibility where permit changes may involve a fairly lengthy amount of approval time.

One of the most flexible scenarios for a bulk drug manufacturing facility is the case where every piece of process equipment at the facility can be operated in any of the permitted processes with notification only requirements when the facility wants to make any changes. On the other hand, the permitting agencies maintain that too much operational flexibility makes it difficult for the agency to understand the facility's applicable requirements and to determine the facility's compliance status on an ongoing basis. Some regulatory agencies have attempted

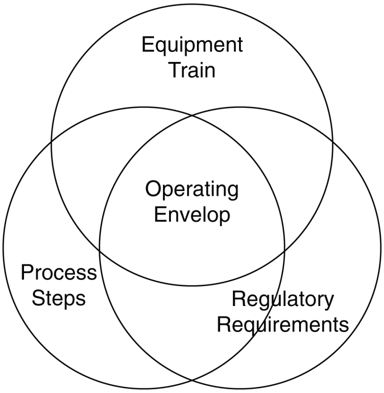

FIGURE 3 The operating envelop is the region created from the overlap of the requirements from the process steps, the equipment configuration within the equipment train, and the applicable regulatory requirements of the jurisdiction where the process is permitted. A flexible operating envelop denotes operational flexibility that allows expeditors permit change while a stiff operating envelop denotes less operational flexibility and more approval time for permit changes.

to balance the needs of the agency and bulk drug manufacturers by creating a multitier permit change mechanism for various classes of changes (such as minor, mid-major, and major) and a corresponding approval time that is proportional to the complexity of the change requested.

XI. MANAGEMENT OF CHANGE

Management of change is one of the greatest environmental challenges to the staff and leadership teams at the bulk drug manufacturing facility and presents a compliance risk, in some cases. For example, two types of changes or risks are discussed in this section—productivity and regulatory—however, a facility should go through a formal process and identify the number of issues and areas of greatest compliance risk to its operations due to the management of change.

Productivity improvements that reduce manufacturing cost and make the drug product available to its customers at an affordable price is one of the great internal drivers at the manufacturing facility. Hence, there are consistent efforts to make incremental yield improvements to various process steps for as long as the bulk drug product remains at the facility. Sometimes known by the acronym PIO (productivity improvement objective) or PIT (productivity improvement target), the environmental challenge raised by continued productivity changes may result in the case where the current process running in the plant is at some variance to the process description submitted to obtain the initial construction and operating permits. One tool to address this potential compliance risk is to ensure that the process change mechanism is transparent and that the technical staffs are in close communication with the environmental staffs responsible for operating permit management. Another tool to address the potential process variance issues is to have the facility conduct, on a periodic basis, a technique called "permit cleanup" where the narrative and details of the process descriptions on file with the regulatory agencies are modified to align with the current process running in the facility.

Regulatory changes are a second source of challenge and risk to the facility in the case where the facility has not kept current with the changes in applicable requirements. This knowledge gap can pose a regulatory risk in that compliance limits or triggers may have been changed to put the facility's current process in a state of "noncompliance." The other problem stemming from the knowledge gap is that the facility may waste time and resources preparing project estimates for future business opportunities, not knowing that the project estimate (cost and scheduling) is unrealistic because the estimate does not yet include the new requirements. The impact of new requirements to the project estimate, in some cases, may lead to the project postponement or cancellation. The tool to address the knowledge gap is to ensure that the facility is vigilant in following the element of the EMS (see the sect. "Environmental Management Systems," Table 1), requiring timely identification of relevant laws and regulations to the facility's operations. The other tool that addresses the knowledge gap is the consistent application of environmental audits by business unit, corporate, or third-party auditors.

XII. SUSTAINABILITY

There are a number of definitions to the term "sustainability" and many questions as to how sustainability relates to a host of related concepts such as corporate responsibility, global corporate citizenship, corporate citizenship, and sustainable growth—to name a few (16–18). Some sustainability observers see an emerging agreement that sustainability is really about the three realms of economic, social, and environmental performance; the three aspects are also known as the "triple bottom line" of people, plant, and profits (19,20). In other words, sustainable manufacturing companies are simultaneously focusing on their products' profitability, impact on the lives of customers/stakeholders, and impact on the environment from the products' development to disposal. There are opportunities across the pharmaceutical value chain for companies to execute sustainability initiatives such as green chemistry development, renewable energy purchasing/generation, energy and water use reductions, packaging waste reductions, and green sales fleet.

Since energy is at the center of bulk drug manufacturing, many pharmaceutical companies have taken special efforts, such as forming global energy teams and setting global energy reduction targets over some specified period of time from a known baseline to purchase and use energy in an efficient manner. In addition to energy goals and management, some pharmaceutical companies have committed to constructing new laboratory and production facilities to the standards of Leadership in Energy and Environmental Design (LEED), which is the benchmark for the design, construction, and operation of high-performance green buildings (21).

The sustainability aspects of energy reductions from fossil fuel combustion are multifaceted and include reductions in criteria pollutants (e.g., fine/ultrafine particulate, nitrogen oxides, sulfur oxides), reductions in greenhouse gases (e.g., carbon dioxide being the principal component), and reductions in fuel purchasing cost (dollars per year).

The public reporting of sustainability goals and accomplishments continues to emerge and be a challenge for the reporting companies and all interested stakeholders; this public reporting is part of the process known as "transparency," which is defined as the openness of a organization to share information about how the organization operates and conducts a two-way, responsive dialogue with its stakeholders (22). The Global Reporting Initiative (GRI) has developed the most widely used sustainability reporting framework that sets out the principles and indicators that organizations can use to measure and report their economic, environmental, and social performance (23). Since the GRI guidelines are quite detailed and designed to accommodate a broad range of organizations, one of the greatest challenges for pharmaceutical companies is to determine which portions of the GRI guidelines apply and whether the company currently collects the data for the report parameters in question. Stakeholders who read a company's sustainability report are attempting to answer the following questions: Is the company making progress on its prior commitments? How does this company compare to its peers? Many of the global pharmaceutical companies are currently issuing corporate responsibility, global citizenship, or sustainability reports that use the GRI guidelines as their reporting framework (24–29).

XIII. GREEN CHEMISTRY INITIATIVES

Benign by design are three words that capture the great tenant of green chemistry. Green chemistry, also known as sustainable chemistry, is the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances (30). Green chemistry applies across the life cycle, including the design, manufacture, and use of a chemical product. In 1990, the U.S. Environmental Protection Agency finalized the Pollution Prevention Act (PPA), and it was from the PPA legislative driver that the green chemistry initiative began to grow and gain attention in academic and industry circles. The road map for the global green chemistry framework was published in 1998 and is known as the Twelve Principles of Green Chemistry (31):

1. *Prevent waste*: Design chemical syntheses to prevent waste, leaving no waste to treat or clean up.
2. *Design safer chemicals and products*: Design chemical products to be fully effective, yet have little or no toxicity.
3. *Design less hazardous chemical syntheses*: Design syntheses to use and generate substances with little or no toxicity to humans and the environment.
4. *Use renewable feedstocks*: Use raw materials and feedstocks that are renewable rather than depleting. Renewable feedstocks are often made from agricultural products or are the wastes of other processes; depleting feedstocks are made from fossil fuels (petroleum, natural gas, or coal) or are mined.
5. *Use catalysts, not stoichiometric reagents*: Minimize waste by using catalytic reactions. Catalysts are used in small amounts and can carry out a single reaction many times. They are preferable to stoichiometric reagents, which are used in excess and work only once.
6. *Avoid chemical derivatives*: Avoid using blocking or protecting groups or any temporary modifications if possible. Derivatives use additional reagents and generate waste.
7. *Maximize atom economy*: Design syntheses so that the final product contains the maximum proportion of the starting materials. There should be few, if any, wasted atoms.
8. *Use safer solvents and reaction conditions*: Avoid using solvents, separation agents, or other auxiliary chemicals. If these chemicals are necessary, use innocuous chemicals.
9. *Increase energy efficiency*: Run chemical reactions at ambient temperature and pressure whenever possible.
10. *Design chemicals and products to degrade after use*: Design chemical products to break down to innocuous substances after use so that they do not accumulate in the environment.
11. *Analyze in real time to prevent pollution*: Include in-process real-time monitoring and control during syntheses to minimize or eliminate the formation of by-products.
12. *Minimize the potential for accidents*: Design chemicals and their forms (solid, liquid, or gas) to minimize the potential for chemical accidents including explosions, fires, and releases to the environment.

Being the first company to gain marketing approval for a new pharmaceutical product is such a critical business objective in the pharmaceutical industry that few, if any, companies can make a research and development commitment that every new product will be developed using green chemistry principles. Once the new molecular entity, or drug substance, is discovered and granted a patent, the patent-holding company has a specified period of time—for example, the United States currently grants 20 years—of marketing exclusivity. A common strategy is for companies to file the discovery process chemistry with the marketing authorization application to gain marketing

TABLE 5 Winners of the U.S. Environmental Protection Agency's Presidential Green Chemistry Challenge in the Pharmaceutical Industry from 1997 to 2008

Year	Company name	Award category	Product generic name	Description
2006	Codexis Inc.	Greener reaction condition	Atorvastatin calcium	Codexis designed an enzymatic process to make the key building block in the synthesis of atorvastatin. The new green process eliminated the fractional distillation of product and reduced the formation of byproducts.
2006	Merck & Co.	Greener synthetic pathway	Sitagliptin	Merck developed a catalytic synthesis which creates 220 pounds less waste per pound of siagliptin manufactured and increases the overall yield by 50%. Company expects at least 330 million pounds of waste avoided over product lifetime.
2005	Merck & Co.	Greener synthetic pathway	Aprepitant	Merck developed a new synthesis for aprepitant using catalytic asymmetric reactions that reduce the number of process steps from 6 to 3 and eliminates 41,000 gallons of waste per 1,000 pounds of aprepitant manufactured.
2004	Bristol-Myers Squibb Co.	Greener synthetic pathway	Paclitaxel	Bristol-Myers uses plant cell fermentation (PCF) as a sustainable technology to replace a semisynthetic process for producing paclitaxel. During its first 5 years, the PCF process is estimated to eliminate 71,000 pounds of hazardous waste. The PCF process also saves energy by eliminating the use of 10 solvents and 6 drying steps.
2002	Pfizer, Inc.	Green synthetic pathway	Sertraline	Pfizer reduces initial 3 step manufacturing process for sertraline to a single step by using a more selective catalyst and the more benign solvent, ethanol. The new process eliminated 1.83 million pounds of waste per year and the need to distill four solvents from the original synthesis.

TABLE 5 (*Continued*)

Year	Company name	Award category	Product generic name	Description
2000	Roche Colorado Corporation	Greener synthetic pathway	Ganciclovir	Roche developed a 2nd generation synthesis for the production of ganciclovir which increased the overall yield more than 25% and doubled the production throughput. The revised synthesis eliminates 2.5 million pounds of hazardous liquid waste and 55,000 pounds of solid hazardous waste per year.
1999	Lilly Research Laboratories	Greener synthetic pathway	LY300164	Lilly developed an alternative synthesis, with one key aspect the use of yeast to replace a chemical reaction, for the production of drug candidate LY300164. The new synthesis eliminates 9,000 gallons of solvent and 660 pounds of chromium waste per 220 pounds of LY300164 produced.
1997	BHC Company (now BASF Corporation)	Greener synthetic pathway	Ibuprofen	BHC developed a 3 step catalytic synthesis (with 80% atom efficiency) to replace a 6 step stoichiometric process (with 40% atom efficiency) for the production of ibuprofen. The material used as both catalyst and solvent is recovered and reused with greater than 99.9 percent efficiency.

Source: http:www.epa.gov/greenchemistry (accessed Jan 2009).

approval; once the marketing approval is obtained, the company can focus on alternative chemistry routes with the goal of making the second- and third-generation chemistry more efficient and cost-effective over the remaining life cycle of the product.

Challenge and recognition programs are used in countries such as Australia, Italy, Japan, the United Kingdom, and the United States to creatively promote the culture and methodology of green chemistry (32–36). In the case of the United States, the Presidential Green Chemistry Challenge (PGCC) began in 1997 and is a showcase for academic and industrial achievements in green chemistry. The PGCC gives awards in five categories: academic, small business, greener synthetic pathways, greener reaction conditions, and designing greener chemicals. Table 5 shows the companies that have won the award from 1997 to

TABLE 6 The E Factor for Various Industry Segments

Industry segment	Annul product tonnage	kg Waste/kg Product
Oil refining	10^6–10^8	<0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5→> 50
Pharmaceuticals	10–10^3	25→100

The E factor is the total amount of waste generated to produce 1 kg of product. There is a thousandfold difference between the lowest and highest E factor across industry segments investigated. The investigator noted that the relatively larger E factors for fine chemicals and pharmaceuticals are reflective of multistep synthesis and the use of stoichiometric reagents rather than catalytic methodologies.
Source: From Ref. 39.

2008 in the category of greener synthetic pathways and greener reaction conditions (36). It also shows the innovation and benefits that pharmaceutical companies have created by using green chemistry principles. The transformation resulting in process step reductions and waste elimination is quite evident for the companies that used second- and third-generation catalytic synthesis to replace first-generation stoichiometric processes.

A number of metrics have been proposed to define the eco-efficiency of chemical processes that calls attention to the amount of waste generated per unit of product produced (37). One investigator proposed a simple and straightforward metric known as the E factor; the E factor is defined as the kilograms of total waste divided by the kilograms of product (38). From a resource utilization perspective, the E factor gives one a relative comparison of the eco-efficiencies across different industry categories. Table 6 compares the E factor among different manufacturing segments and indicates that the pharmaceutical industry is extremely inefficient relative to other sectors investigated.

In the spirit of the E factor definition, a number of companies belonging to the Pharmaceutical Roundtable, which is part of the American Chemistry Society's (ACS) Green Chemistry Institute®, developed a green chemistry metric called the process mass index (PMI), which is a ratio of raw materials input to bulk API output (39). Figure 4 contains the precise definition of terms used to calculate the PMI. The PMI was developed so that member companies of the Pharmaceutical Roundtable can use a consistent definition and be able to benchmark processes across different companies. Seven Pharmaceutical Roundtable companies recently agreed to participate in a benchmarking study where the blinded data from 46 processes were submitted for analysis. Table 7 shows the range of PMI values for the collective 46 processes and the median PMI for the 46 processes by developmental phase from preclinical to commercial. With respect to the collective 46 processes, the median PMI was 120 with a minimum of 23 kg and a maximum of 887 kg material use per kilogram of API. Table 7 also shows an impressive 76% reduction in median PMI from the preclinical to the commercial phase. The composition of PMI for the 46 processes reveals that almost 80% is solvent and water (solvent 49% and water 28%) while reactants were 9% (39).

Process Mass Intensity Metric From Pharmaceutical Roundtable At ACS Green Chemistry Institute
$$\text{Process mass intensity} = \frac{\text{quantity of raw materials input (kg)}}{\text{quantity of bulk API out (kg)}}$$
Where:
Process is all steps of a synthetic path from commonly available materials to the final bulk active pharmaceutical
Raw Materials are all materials including water that are used directly in the process of synthesizing, isolating, and purifying the API salt
Bulk API out is the final salt of the active ingredient that was produced in the synthesis, dried to the expected specification

FIGURE 4 Member companies of the Pharmaceutical Roundtable at the ACS Green Chemistry Institute proactively established a common green chemistry metric definition to enable benchmarking and to have a more transparent basis for comparison to help drive change and define possibilities for member companies. *Source:* Henderson R.K., Kindervater J., Manley J.B. Lessons learned through measuring green chemistry performance—The pharmaceutical experience http://chemistry.org/greenchemistryinstitute/pharma_roundtable.html (accessed Jan 2009).

TABLE 7 Results from Benchmarking of 46 Processes Provided by 7 Pharmaceutical Companies Participating in The Pharmaceutical Roundtable at the ACS Green Chemistry Institute Show the Progress that Some Companies Are Making in Reducing Their Median PMI

Phase	**No. of processes**	**PMI median** (kg Material Use/kg API)
Preclinical	7	185
Phase 1	5	123
Phase 2	13	117
Phase 3	16	96
Commercial	5	45
Process Mass Intensity (PMI) for 46 processes		
Minimum (kg Material Use/kg API)	**Median** (kg Material Use/kg API)	**Maximum** (kg Material Use/kg API)
23	120	887

From the preclinical to the commercial phase, there is a 76% reduction in the median PMI for the 46 processes examined.

Abbreviation: PMI, process mass index.

Source: Henderson R. K., Kindervater J., Manley J.B. . . Lessons learned through measuring green chemistry performance—The pharmaceutical experience
http://chemistry.org/greenchemistryinstitute/pharma_roundtable.html (accessed Jan 2009).

The results from the benchmarking study show that the companies are making real progress in greening the development process. The benchmarking study will be repeated on a periodic basis, and the Green Chemistry Institute is encouraging its pharmaceutical members to submit more data to increase the size of the benchmarking database. One of the implications of the new metric may be that some bulk drug facilities begin using the PMI to prioritize the existing process at their facilities to evaluate incremental PMI improvement opportunities. It should give pause to many that the pharmaceutical industry has the highest waste generation per pound of product produced and the highest amount of organic solvent used per pound of product produced for any commercial sector (40,41). The use of high-pressure water sprays and detergents are being investigated and used by some pharmaceutical companies as an alternative to the use of organic solvents for vessel cleanouts.

XIV. CONCLUSIONS

The effort that an organization expends to ensure that its bulk drug manufacturing processes are in regulatory compliance with all emissions limits and work practices is a task of increasing complexity. High-performing organizations use the license-to-operate model as the strategic framework to guide its outreach to key external stakeholders—such as environmental regulators, local political leaders, students, neighbors, NGOs, and other interested parties—about building and maintaining trust. The trust-compliance connection means that increased compliance leads to increasing trust while noncompliance leads to decreasing trust. A tool such as a robust EMS helps a facility systematically execute on its environmental goals and objectives.

In addition to its compliance focus, the leadership and staff at the facility must also understand the corporation's sustainability goals and programs. The notion of thinking globally and acting locally becomes the guiding principle in helping the facility identify approvable sustainability projects, obtaining project funding, and documenting project outcomes. Global energy and water reduction initiatives are being reported by pharmaceutical companies in absolute and normalized (to sales) terms. Facilities should become familiar with the GRI reporting system since the GRI is the most widely used reporting framework for sustainability. Organizations are encouraged to evaluate the feasibility of using PMI in identifying and prioritizing solvent reduction opportunities for existing processes. The use of high-pressure water sprays and detergents may be a viable alternative for some processes that are currently using organic solvents for vessel cleanouts.

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10 Thermochemical Process Safety—An Introduction

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I. PREAMBLE

The concept of chemical processing responsibility at large was introduced in chapter 2, section "New Trends and Their Probable Impact on Bulk Drug Process Development," including a discussion of ***thermochemical hazards*** in processing and ***thermochemical process safety*** as one of the three components of responsible chemical processing, the others being environmental protection and industrial hygiene. Indeed, the reader is urged to review that material by way of preparation for the different treatment to follow herein, since repetition will be avoided except when necessary for providing a comprehensive context.

> ***A reminder***: Throughout this chapter, as in chapters 2 and 3, we will often refer to ***our context*** and to ***pharma***. In both cases we abbreviate ***the context of chemical processing of fine chemicals, drug intermediates and bulk drugs (i.e., APIs)*** so as to more precisely state where our content applies, for many of the specifics are unique to the milieu and scope of ***pharma***.

In this chapter, we will focus on the ***assessment*** of thermochemical hazards during process conception and development and, to a lesser extent, on the scale-up and process design for addressing those hazards that, once assessed, may be accepted as part and parcel of the process to be implemented. The specifics of the practice of thermochemical process safety in process design and operation will be addressed in chapter 11 within its broader context of process safety. Nevertheless, if we err, it will be on the side of perhaps overlapping some content.

> Thermochemical hazards, as discussed in chapter 2, section "New Trends and Their Probable Impact on Bulk Drug Process Development," are those arising from the energy released by chemical reactions, whether intended of not. As we will see, such ***thermochemical energy***, if not well controlled, may create all manner of hazards, each with its own range of risks and possible consequences.

At this point, before we go into a discussion of thermochemical energy, it seems useful to refresh our understanding of ***energy as a property of mass***. The energy of a mass at the molecular level is most easily viewed as that defined by the motion of the mass molecules—for example, their velocity in a gaseous mass, their lesser velocity in a liquid mass, or their very limited mobility in a solid mass. Nevertheless, we should go a bit deeper into our understanding of energy, even if eventually we will seek some simplifications when it comes to thermochemical energy and its crucial, but not so well understood, manifestation—***heat***, thus the presentation of Table 1, with brief qualitative descriptions of the various forms of energy. Coming in so many diverse forms, energy can be elusive to our grasp, which prompted the creators of thermodynamics to define it ***quantitatively*** and ***precisely*** through mathematical expressions that, as it turned out, describe well the observed experimental facts of phenomena

TABLE 1 Energy and Its Forms

Recall the various forms of the energy property of a mass and its transformation, each measured in units that are interconvertible, just as degrees centigrade and Fahrenheit measure another property of a mass, that is, its temperature.

Mechanical	
Potential such as (weight) × (height)	**Relative to a plane of reference to which the mass could fall**
Kinetic = **(½) × (mass) × (velocity)^2**	**Gained by a mass as a force imparts velocity or lost as velocity goes into work or friction**
Work = **(force applied) × (distance)**	**For example, *energy spent* lifting a mass**
Other than mechanical	
Heat, which is:	**Energy *in transit*, as transferred by contact between masses at different temperatures and measured as one mass gains energy by (mass) × (temperature change) × (proportionality constant[a]). Also from mechanical energy (e.g., by friction), from the *latent heat*[b] of a condensing vapor, chemical reaction, electrical current through a resistor, or thermal radiation (e.g., sunlight)**
Chemical	**(Moles reacted) × (energy change per mol)—released or gained as *heat* upon chemical reaction (i.e., reactants go to products)**
Other forms of lesser interest herein—electrochemical, light, nuclear, etc.	

[a] The proportionality constant is the ***heat capacity C_p***.

[b] The latent heat is that from a phase change (fusion, evaporation, crystallization, melting, condensation, dissolution, etc.).

involving energy. Indeed, most key thermodynamic properties of a mass system are defined by equations, although we often seek and use less precise, but more manageable, definitions by a less rigorous use of the fundamental equations. Such will be the case with thermochemical energy in our context—organic chemical synthesis of bulk drugs—in which taking some reasonable liberties with the applicable equations works well enough.

> Let us add in closing this introduction that the energy of a system, unlike its mass or its volume, cannot be known in absolute terms but only relative to some arbitrary reference state of the system. Indeed, all we care about are the ***changes in the energy of systems between their initial and final states***, and we refer to the chosen reference only to help us measure or calculate the magnitude of the changes.

II. HAZARDS, RISKS, AND CONSEQUENCES—DEFINITIONS AND AN ACTUAL THERMOCHEMICAL EXAMPLE

Some definitions from chapter 2 merit restatement, for they undergird the content of this chapter.

Hazard—a source of danger, possible injury, or loss
Risk—the probability of suffering a given loss or injury from a hazard

The above definitions imply that a given hazard may pose different risks, which is indeed the case. Consider then a simple example that should make the point:

Case 1—A truck, loaded with paper goods and traveling at 50 mph on a narrow and undivided country road presents a finite hazard of colliding with another vehicle or coming off the road, probably turning over.

Case 2—The same truck at the same speed and on the same road but carrying a load of chlorine containers (filled to capacity, with chlorine as a liquid under its high vapor pressure) presents a greater hazard, namely, on collision or turnover, one or more of the chlorine cylinders may rupture and release an amount of chlorine that will disperse as a toxic gas from the accident site.

Case 3—The same truck at the same speed and on the same road, loaded with chlorine cylinders, enters an inhabited hamlet that occupies both sides of the road for a short stretch. The hazard of a collision or turnover, and potentially causing a release of chlorine, is comparable to that of Case 2.

Thus, on the basis of the previous definitions, we can rank the hazards and their risks as follows:

$$(\mathbf{Hazard})_3 = (\mathbf{Hazard})_2 >> (\mathbf{Hazard})_1$$

$$(\mathbf{Risk})_3 >>>> (\mathbf{Risk})_2 >> (\mathbf{Risk})_1$$

What the above rankings say about the risk arising from a given hazard is that the specific circumstances at hand *and* the potential consequences of the same mishap define the risk. Assuming there is no other road to travel on, **(Hazard)$_1$** is unavoidable, but we can reduce its associated **(Risk)$_1$** by, say, traveling at a slower speed. But once we transport the chlorine cylinders, we not only qualitatively increase the hazard by the potential of chlorine release, that is, **(Hazard)$_2$**, but also inevitably create a greater risk of harm to all the people involved in the mishap or that might happen to be about, that is, **(Risk)$_2$**. Then, if we consider the same hazard of a mishap while traveling through the inhabited hamlet, as in Case 3, we have quantitatively increased the risk of harm by the greater number of people that might be exposed, that is, **(Risk)$_3$**.

This distinction between a hazard and its potential risks is crucial to the practice of thermochemical process safety, for often ***we must implement processes with known hazards*** and do so at an acceptable level of risk by skillful assessment of the latter and the no less skilled implementation specifics: good process design, safeguards of process control, containment of process streams, and, in the extreme, abatement provisions for materials that might be released from the process on a mishap or, additionally, location of the processing activity far from populated areas. In assessing the risk of a hazardous process operation (e.g., running a chemical reaction with known thermochemical hazards), both the probability of a mishap and the severity of the consequences need to be considered in order to finally assess if the risk of a specific process operation is acceptable or not (1, chap 1).

To further illustrate this crucial point we will now examine an actual chemical processing mishap that had major consequences—the 1976 Seveso incident, one more wake-up call that, alas, was not heard and paid heed to by all soon enough. For, a few years later, the chemical industry had to confront a related and far greater catastrophe that caused thousands of human fatalities—the 1984 release of ~25 tons of methyl isocyanate (a toxic volatile chemical) in the vicinity of the town of Bhopal in India (2). But returning to the earlier Seveso mishap, let us now carefully consider Figure 1, in which we summarize the chemistry at play and the unfortunate events of that occasion.

The extreme toxicity and persistence of the dioxin compound were well known from previous mishaps (1957, 1963, 1968) in the manufacture of trichlorophenol, mishaps that resulted in significant amounts of dioxin (as a contaminant of process materials) escaping processing vessels, followed by illness of over 200 workers who were variously exposed, of which four died of dioxin poisoning and a fifth died from the explosion of the reaction mass in the 1968 incident (3,4). Further, the last of those earlier mishaps came about from a known thermochemical hazard of the chemistry—the large energy release of the final reaction mass at elevated temperature, the result of ***unintended*** reactions not involved to a significant extent at the normal temperatures of the trichlorophenol process. Alas, eight years later the Seveso plant was not adequately equipped or operated to deal safely with the known thermochemical hazards of the synthesis of trichlorophenol (4). Granted, the potential to overheat the reaction mass seemed improbable given the reactor heating scheme (using saturated steam at a chosen pressure of 12 bars), thus fixing the temperature of the heating medium at a maximum value ~30°C below the known onset temperature of the decomposition. Nevertheless, the overall plant scheme for efficient energy use relied on process steam obtained by bleeding from superheated steam in the plant powerhouse. Alas, the abnormal shutdown of the trichlorophenol batch on the evening of Friday 09 allowed the partially worked-up batch to sit for hours while inadvertently exposed to an ***unintended*** heat input from much hotter steam [at least 80°C *above* the onset of decomposition (4)], which reached the dome and upper walls of the vessel and then heated the upper part of the unstirred process mass by radiation and some conduction, setting off its decomposition and then that of the total batch, all with the consequences described in Figure 1.

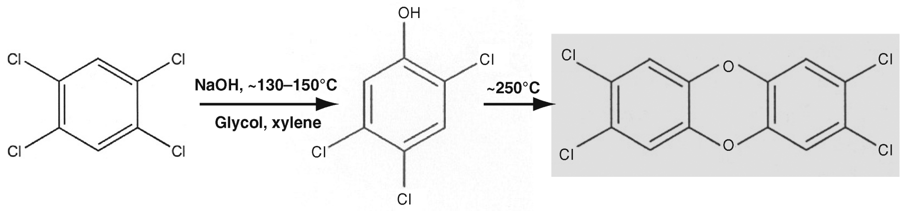
Thus, the happenstance of the Friday night shutdown (as opposed to completing the work-up and cooling to secure the batch on overtime), coupled with the potential exposure to an abnormally hot steam source [a weekend peculiarity due to the lesser demands on the steam turbine (4)], led to a very rapid and large release of thermochemical energy and a vessel overpressure that was relieved—successfully preventing rupture or even explosive failure of the vessel—through a system that was ***vented directly into the open***, as per Figure 2. At this point we can revisit the points made about hazard, risk, and consequences by analysis of the incident:

a. The trichlorophenol reaction proper did not present a thermochemical hazard, and the reaction is meant to be driven to its end point at ~150°C by heating under temperature control. Cooling need not be applied during the reaction cycle.
b. The reaction mass did present a clear thermochemical hazard all the way through the subsequent distillation work-up—a large and rapid release of energy in the event of abnormally high temperature, as in the 1968 incident—with an onset ~60°C above the highest intended temperature for distillation work-up.
c. The first line of defense—limiting the temperature exposure of hazardous process materials—was breached by two factors:

   – Lack of a safe shutdown procedure. A hazardous process mass (as per b above) should not be left standing hot and unattended for a long period of time. Indeed, it is a general rule to keep such materials far below the onset of the hazardous condition. As we will see, sometimes the *actual* onset of

The Seveso incident, 1976
A dormant hazard, a risky context and the severe consequences

This incident took place following completion of the reaction to make 2,4,5-trichlorophenol and partial distillation work-up. The reaction mass was left at rest (no heating or stirring) over the weekend, but, inadvertently, superheated steam did reach the piping and valve feeding the internal steam coil of the vessel. Although no steam passed into the coil, enough heat passed by conduction to the upper part of the vessel and then by radiation and conduction to the unstirred reaction mass.



1,2,4,5-tetrachloro-benzene

2,4,5-trichlorophenol

2,3,7,8-tetrachloro-dibenzoparadioxin ("dioxin")

On Sat 10 July the unattended reaction mass underwent a runaway exothermic decompositiion, with the development of enough pressure to expel a good portion of the batch through the pressure relief system at a time of windy weather and subsequent rain. An area downwind from the plant (~10 sq. miles) was contaminated by deposition of the released material (with an estimated 2 kg. of the dioxin).

The dioxin byproduct (highlighted), although normally a trace impurity, was formed to a much greater extent during the temperature excursion, and it was eventually found in the blood of inhabitants of the area, hundreds of which developed chloroacne, a skin disorder previously linked to exposure to dioxin. In this incident there were no human fatalities, but many farm animals died, decontamination og buildings and soil in the affected area was extensive, and so was the public health effort for examination, diagnosis, treatment and long term monitoring involving thousands of area inhabitants.

FIGURE 1 The Seveso incident, as it became known in the chemical industry, illustrates well the core issues of thermochemical process safety in this chapter.

heat release occurs at temperatures lower than those indicated by screening tests, and when such tests show a major heat release, a more rigorous test is indicated to ferret out the actual onset temperature. Failing that, a greater distance between the safe process envelope and the hazard is indicated (see chap. 2, Fig. 21) with an upper indent in proportion to the probability and severity of the risk.

- Failure to recognize that the weekend circumstances of the steam source allowed for much hotter steam to reach the point from which heat could be transferred to the process vessel during the shutdown condition. This may seem a bit of a stretch, since the normal operating schedule did not call for a batch to be held hot over the weekend. Nevertheless, a more rigorous ***risk analysis*** of the operation should have ferreted out the possibility of the two abnormalities occurring at the same time and a safer shutdown procedure adopted.

There was, however, a more basic failure—the trichlorophenol process could have been set up with a more secure stepping down of the steam pressure, one that made it impossible for superheated steam to even come close to the process. Finally, to the worst failure: the lack of provisions to contain the highly

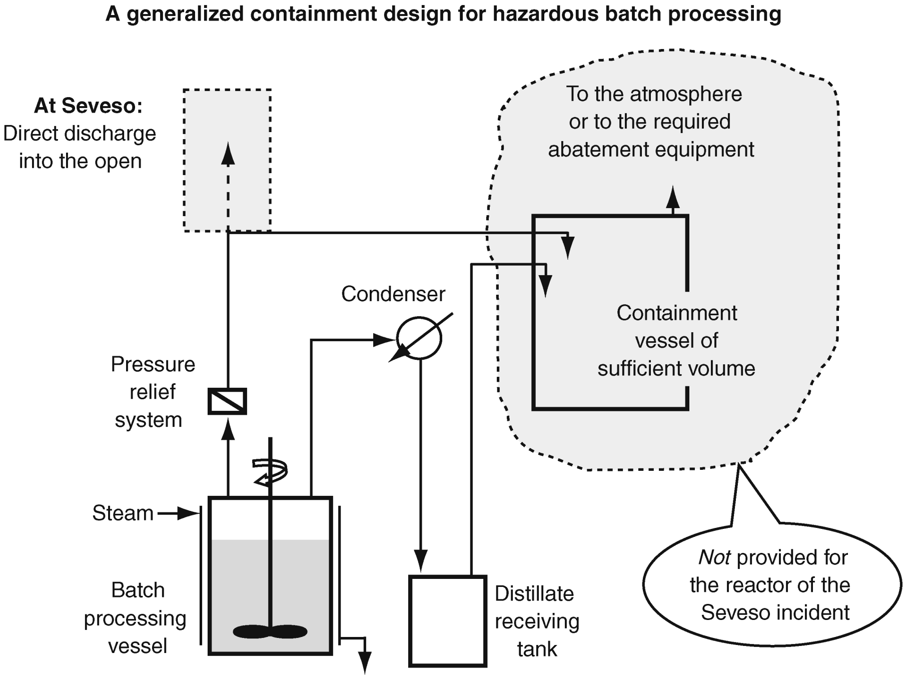

A generalized containment design for hazardous batch processing
At Seveso:
Direct discharge into the open
To the atmosphere or to the required abatement equipment
Condenser
Containment vessel of sufficient volume
Pressure relief system
Steam
Batch processing vessel
Distillate receiving tank
Not provided for the reactor of the Seveso incident

FIGURE 2 The risk assessment of the trichlorophenol operation must have failed to weigh the severity associated with the risk of release into the open from relief venting of the reactor, since the extreme toxicity of dioxin was well known from the previous accidents with the same process.

toxic process material in the event of an overpressure discharge. The pressure relief system of the reactor operated as intended and prevented a violent vessel rupture, but its discharge into the open was a fateful omission of process design, given the predictable risk of dispersing the highly toxic dioxin. Recall that all three previous mishaps with escape of dioxin revealed its very high toxicity and its severe consequences to personnel, even to those exposed during the clean-up after the 1963 release (3,4,5). The missing containment provision was addressed by one of the broad rules in the so-called "Seveso Directive" (6), promulgated later in 1982 by the European Union for the prevention of chemical processing accidents and their consequences. A general design that would have prevented the environmental release and wide dispersal of so much dioxin at Seveso is depicted in Figure 2—a process design ***circumstance*** that would have drastically ***reduced the risk*** of the worst mishap arising from the thermochemical hazard of the process. Given the known formation of much dioxin upon a temperature excursion and the toxicity and persistence of the compound, the teachings illustrated in Figure 21 in chapter 2 should have been brought to bear on the design and operation of the process, namely, set up the operation with a ***contoured process envelope*** that takes into account not just the probability of a risk but also the severity of the consequences. We will return at this point in the context of the previously cited Bhopal catastrophe in 1984.

III. THERMOCHEMICAL EVENTS AND THEIR BASIS—ENERGY

Most chemical reactions are accompanied by either the release of energy or the gain of energy—the thermochemical events ***inevitably*** associated with the transformation of reactants into products. Absent the use of a significant part of the energy for the performance of mechanical or other work on or by the chemical reaction mass, in our context of chemical processing the total energy released or gained, is manifested ***only as heat***; that is, thermal energy coming, going, or being assimilated by the reaction mass and that in all cases requires that it be managed safely or actually prevented if it might arise from unintended reactions by a processing abnormalities or other mishap.

> ***Heat is energy in transit*** (Table 1), being gained or released by a mass in various ways: released from a hot mass to a cool mass, released or gained by a chemically reacting mass, gained by fluid from the energy spent by a tank stirrer or pump impeller, or, as in the Seveso misfortune, radiated and conducted from a hot metal mass to a less hot process mass.

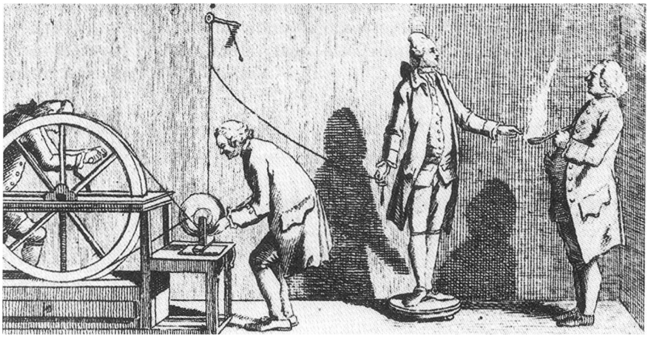
If heat is energy in transit, which it really is, then we err when we refer to a mass as having this or that much heat. Instead, the mass has this or that much ***energy***. If we contact it with a cooler mass, energy will be transferred as 100 percent heat from the former to the latter, with a corresponding decrease and increase in the energy content of the former and latter masses, respectively. Alternatively, we can use the same mass as a counterweight in a pulley and do ***work*** (i.e., energy) to lift a bucket of water from the depth of a well at the expense of the potential energy lost by the mass. In this case, however, most of the energy will be ceded to do mechanical work (the weight of the bucket times the distance it was raised), with the small remainder dissipated as heat by the friction losses in the pulley.

> That ***energy***—from the Greek for ***activity***—is an interconvertible, transferable, and useful entity and was known in a strictly qualitative sense well before the pioneers of thermodynamics addressed it with rigor and insightfulness. This is apparent in an engraving dated ca. 1774 (7), shown in Figure 3, and the reader is invited to sort out the various forms of energy being converted (from left to right) with the aid of Table 1.

A series of experiments along this interconversion concept was conceived by Joule, who ca. 1845 demonstrated that energy as mechanical work can be consistently transferred as heat to a fluid (Fig. 4), not only confirming much earlier work (ca. 1800) by Rumford [(8), pp. 3–12], but also obtaining, due to his experimental skills, a reliable interconversion factor between mechanical work and its energy equivalent transferred as heat [(8), pp. 24–39]. Indeed, Joule himself and others had already demonstrated, although not as elegantly, the interconversion between electrical energy and mechanical work and that between electrical energy and heat. Thus, by 1850 the concept of the conservation of energy and its interconversion among its many forms was firmly established to eventually become the First Law of Thermodynamics [(8), p. 33].

Yet, why all the fuss here about the words "energy," "heat," and "work"? That issue has been long settled and is the basis of the First Law of Thermodynamics, which can be stated in a various ways (Fig. 4) but all based in the same experimental fact: ***energy, when all transformations for all its forms are***

Energy is so interconvertible!
(as represented in a 1774 engraving)



Man holding a flammable fuel in a spoon. Ignition has taken place as per the flame.

Man operating the crank of the large wheel.

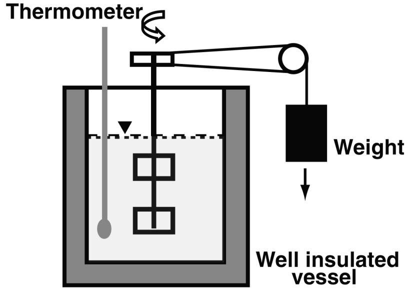
Man pressing a suitable material against the faster small wheel.

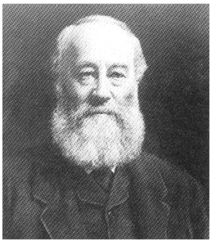
Man acting as a conduit for the electrostatic charge.

FIGURE 3 An amusing depiction of the fact that energy, even if vaguely understood at the time, was known to be interconvertible before the first fundamental insights into the phenomena involving energy were gained. *Source*: With permission of John Wiley and Sons, Inc.

Interconversion of heat and mechanical work

Recall Joule, who in 1843 determined the proportionality between heat and mechanical work by measuring the temperature rise in an ***insulated*** body of water as it was stirred with paddles driven by falling weights. Joule unambiguously demonstrated ***the interconversion between the two forms of energy***.





James P. Joule, British, 1818–1889

First Law of Thermodynamics—***The total energy of an isolated system is constant.*** When coupled with the interconvertibility of the various forms of energy, the First Law can restated in simpler terms:
Energy is not created or destroyed. It is conserved.

FIGURE 4 Joule and his simple apparatus yielded the first quantitative insight into the conservation of energy.

added up, is conserved across all phenomena (except those that involve fission or fusion of the atom). So how do we come to grips with the experimental fact that chemical reactions are most often accompanied by heat release or heat gain? When there is a release, where is the energy coming from? And when there is a gain from the surroundings, where is it going to? Such ***heat effects*** range from the negligible to the large, sometimes so large and so rapid as to make the reactions ***hazardous*** to carry out at sufficient scale. And what about the potential for the significant mechanical work component as part of the energy releases from chemical reactions (e.g., the combustion of fuel by a spark inside a piston in an engine)? Thus the development of thermochemistry as a field straddles chemistry and thermodynamics, for the latter demands that chemical reactions conform, as all other phenomena, with its fundamental and inescapable laws. Fortunately, those that built the formidable edifice of thermodynamics did so by defining properties of material systems that were most useful in the study and applications of energy and its myriad of transformations, thus making sense of it all with due rigor and enabling the quantitative approach to the understanding of all energy phenomena.

Let us first consider the driving force of a chemical reaction and the resulting energy releases or gains—the so-called ***heat effects*** already mentioned—when reactants are transformed into products. To keep us from getting involved with the far more complex Second Law of Thermodynamics, we will wave our hands and simplify matters, although we need to deal with some definitions that can only be properly expressed by their equations. Indeed, thermodynamics is based on mathematical definitions of properties conceived in order to adequately describe the phenomena involving energy and its transformations. As a tribute to a good many scientists, largely from the 19th century, their definitions work exceedingly well, enabling us to predict the behavior of all manner of phenomena and develop applications thereof—catalytic reactors, separation processes, power plant machinery, process equipment, novel products, etc. But our awe is making us digress. Let us return to the fundamental questions: ***What drives chemical reactions—from reactants to products? What are those reservoirs of energy that make certain reactions release heat? What are those sinks of energy that make others absorb heat as they take place, thus requiring it?***

The property that may be best used to describe the behavior of chemical systems (including reactions and their equilibria) is the *free energy G* (for J. W. Gibbs, 1839–1903, physics professor at Yale). Since we are only interested in the ***change*** of this property across a chemical reaction (from the initial state of reactants to the final state of products), Gibbs wrote:

$$\textbf{Change in the Free Energy of a chemical reacting system} = \boldsymbol{\Delta}\mathbf{G} \quad (10.1)$$

Then, from the ***definition of G***, as per Gibbs:

$$\boldsymbol{\Delta G} = \boldsymbol{\Delta}\textbf{\textit{Energy}} + \textbf{pV Work} - (\textbf{Temperature in }^{\circ}\textbf{K})(\boldsymbol{\Delta}\textbf{\textit{Entropy}}) \quad (10.2)$$

And here is where the waving of hands starts. First, for chemical reactions *not* taking place at elevated temperatures, well beyond the range of the reactions in our processing context, the last term involving the ***entropy*** property is usually not significant, which conveniently (and mercifully for our scope herein) allows us to avoid dealing with entropy, a thermodynamic property defined mathematically so as to deal with the experimental fact that the "usefulness" of energy diminishes with every transformation. Thus we drop the last term of equation (**10.2**), which leaves us with:

$$\Delta G = \Delta \mathit{Energy} + \mathbf{pV}\ \textbf{Work done by the system} \tag{10.3}$$

Another waving of hands is possible, since most of our liquid phase chemical processing takes place at relatively constant pressure and with small changes in volume upon chemical reaction; that is, *unlike* the explosion of dynamite (the blast and the shock wave do a good deal of pV work) or the combustion of gasoline in an internal combustion engine (with pV work to displace the piston), carrying out chemical reactions in pharma ***hardly ever*** involves significant **pV** work, further reducing our equation of interest to:

$$\Delta G = \Delta \mathit{Energy} = \Delta E \tag{10.4}$$

The above equation, albeit a convenient simplification, can be applied soundly to practically all the chemical reaction systems in our pharma context (no pV work, no elevated temperatures). The value of the free energy function G and its all-important change ΔG across a chemical reaction can be visualized through a simple model (which *we* will call the Gibbs pictorial model) of the course of a chemical reaction, and we leave it to Figure 5 to more fully explain the events depicted, and will just emphasize here that the ***reaction coordinate*** is nothing more than a clever means of depicting the course of a chemical reaction at the molecular level—reactant molecules at the left, transient intermediate molecules in the middle, and product molecules to the right, with the course of

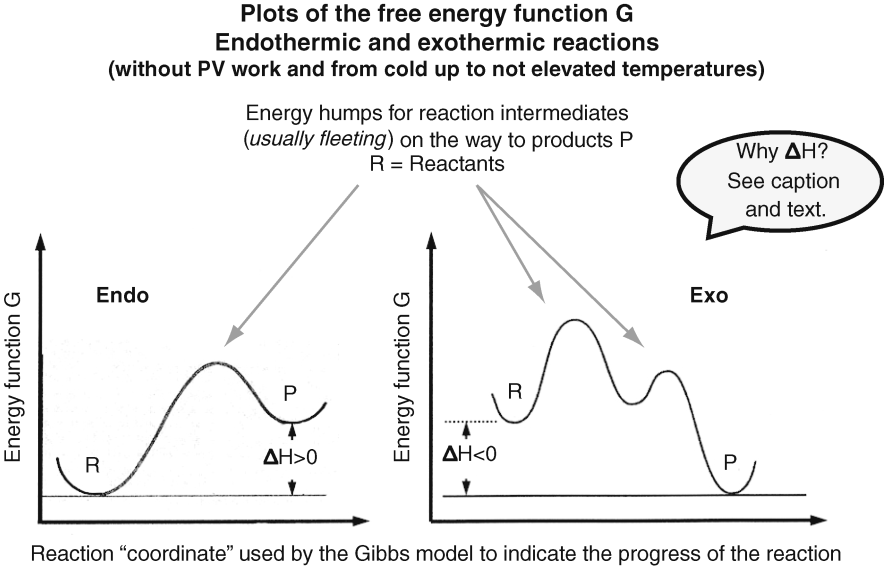

Plots of the free energy function G
Endothermic and exothermic reactions
(without PV work and from cold up to not elevated temperatures)
Energy humps for reaction intermediates
(usually fleeting) on the way to products P
R = Reactants
Why ΔH?
See caption
and text.
Endo
Exo
Energy function G
Energy function G
R
P
ΔH>0
R
ΔH<0
P
Reaction "coordinate" used by the Gibbs model to indicate the progress of the reaction

FIGURE 5 Gibbs's free energy and transition intermediates hypothesis as depicted along the not-so-imaginary reaction coordinate as a model for chemical reactions and their energy manifestations.

the reaction proceeding from left to right, as reactant bonds are undone and turn into the new bonds of the products, almost as in a slow leftward motion so we can see it happen.

> There are reactions that can be practically visualized as taking place along the reaction coordinate of Figure 5, such as the conversion of methyl chloride to chloroform, and the more curious reader can go to Solomon's textbook [(9), sect. 6.6–6.12] for an excellent discussion of the free energy changes, transitions, and the free energy plots as per Figure 5.

The free energy axis, upon acceptance of equation (**10.4**) as our working equation for thermochemical events, allows depiction of the energy course of the reaction on the left side of Figure 5—an ***endo***thermic reaction with a positive change in energy content of the system; that is, the system ***gains*** energy from its surroundings ***or*** by trading some of its own thermal energy for the greater chemical energy of the reaction products (i.e., the reaction mass ***cools down***). For an ***exo***thermic reaction that releases energy, shown on the right side of Figure 5, the change in energy content is negative (***products have less energy content than reactants***) and the energy released is given up as heat to the surroundings *or* traded for greater thermal energy of the reaction mass (it ***warms up***), just the opposite of the endothermic case.

> The established convention in thermodynamics and related fields (e.g., thermochemistry) is that changes in any key thermodynamic property of a mass system is determined ***by subtracting the initial state value from the final state value***—energy gains are positive; losses are negative. In our case, we subtract the property value of the reactants system from the value of the products system.
>
> The thermodynamic properties ***at issue herein*** were defined so that the magnitude of their change is independent of how it came about (i.e., the pathway), depending only on the difference between the initial and final states. This, as we will see, a most convenient attribute for our thermochemical pursuits that was sort of foreseen and put to use by a certain chemist, G.H. Hess, well before the said properties were defined.

Also depicted in Figure 5 is the fact that most reactions go through intermediate stages, ***usually*** so fleeting that highly specialized methods are needed to detect or infer their existence. The depictions in Figure 5 also show these stages for the cases when the reaction may not proceed spontaneously at a significant rate—that is, the intermediate stage has a higher energy content than the reactants, and the latter need to be activated with energy to allow them to reach the intermediate state(s) from which the descent to the less energetic products can take place. Such "energy humps" are common in chemical reacting systems, which explains the need for so often having to increase the temperature and get the system up and past the energy "hump." The reader wishing to learn more on this topic is encouraged to revisit the material in Ref. 9 and study chapter 9 of the book by Keeler and Wothers (10).

Now we still have to address a question raised in Figure 5. ***Why ΔH rather than ΔE?*** Well, the reason is simply one of conventions and our desire not to put the reader at odds with those conventions as used in thermochemistry and in thermodynamics at large. Because it turns out that another very convenient property—***enthalpy H***—has been defined as:

$$\boldsymbol{H} = \boldsymbol{E} + \mathbf{pV} \tag{10.5}$$

Where pV is the product of the pressure P and volume V of the system, and when either of these variables changes significantly, as in the case of a gas being compressed in a piston, the change in **pV** is mechanical work, another form of energy that can expressed in units consistent with those of ***E*** (do recall Joule's work in Fig. 4).

Obviously, such property is most useful when dealing with systems in which pV work is done (e.g., steam turbines, compressors, refrigeration machinery) and, as exceptions, in chemical reaction systems that do pV work (again, the combustion of fuel by a spark in the piston of an internal combustion engine or the use of explosives when building a dam). The exceptions notwithstanding, all the thermochemistry literature describes thermochemical events by their ***enthalpy*** changes ΔH even when the pV term is negligible, as it is in our context. All this means to us is that the ***heat effects*** of chemical reactions—releases or gains—will be called ***enthalpy changes*** ΔH. This explains the ΔH values in Figure 5.

Endothermic **reactions with a heat gain as they proceed:** $\Delta H > 0$
Exothermic **reactions with heat release as they proceed:** $\Delta H < 0$

This seems an opportune place to quote from the classical text of Dodge (11):

> "Many processes of industrial importance occur at constant pressure ***(and volume)***, and to obtain a value for the heat evolved or absorbed in such a process it is necessary only to subtract the values of ***H*** for the two terminal points of the process." Please note that the reference to volume (in ***italic***) has been audaciously inserted by this author.

The above statement by Dodge describes a relatively simple method of estimating and otherwise manipulating the values of the heat effects of chemical reactions. Indeed, many in the literature still use ***heat content*** as equivalent to ***enthalpy*** even when we know heat is ***not*** contained by a system; ***energy is***. No wonder Professor Mark Zemansky, City College of New York, is so fond of the following ditty (12):

Teaching heat is as easy as a song.
We make it simple by teaching it slightly wrong.

IV. THERMOCHEMISTRY, HEAT EFFECTS IN CHEMICAL REACTION PROCESSING, AND CALORIMETRY

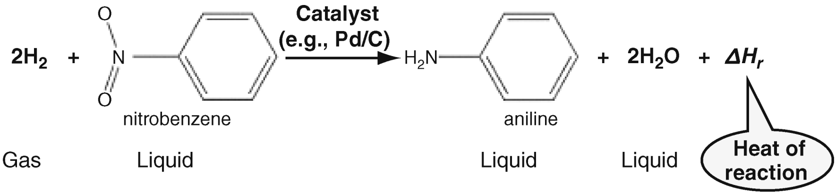
A. Thermochemistry

We need to briefly review the ABCs of ***thermochemistry*** before we embark on our discussion of thermochemical hazards and their assessment, since thermochemistry and its methods are the foundation of such assessment. Even as the richness of chemical structural features of bulk drugs and their intermediates precludes the direct use of the early methods, understanding the latter is useful to our understanding of the thermochemical events of a processing step or series of steps. Indeed, we are keenly interested in capturing the ***onset conditions, rate, and magnitude*** of all significant heat effects across the various processing steps, ***not just those of the principal reactions of interest***.

As Figure 5 hopefully made clear, the energy sources and sinks in chemical reaction systems arise from the different energies used up or released as we undo and make chemical bonds, and as these releases and absorptions are added up with their corresponding + or – signs, the net result is the ***enthalpy change*** ΔH (or to put it "slightly wrong," the change in ***heat content***) as reactants are converted to products. We are aware of the chemical energy reservoirs associated with chemical bonds through observations we make when some of those bonds change with very apparent energy release—the scratching a match against a rough surface, the flame so hot that some of the energy release results in light, as at the end of the sequences in Figure 3. Conversely, in the acid catalyzed decomposition of some *t*-butyl esters into the carboxylic acid and isobutene gas, the latter stops coming off as soon as the heat input is denied, or the hydration reaction upon dissolving solid $ZnCl_2$ results in a chilled aqueous solution. Thus, some reactions are endothermic and some are exothermic; but the latter are the ones that create ***thermochemical hazards***.

Let us continue by defining and understanding the ***enthalpy change*** $\boldsymbol{\Delta H}$ ***of a single chemical reaction***, which we will consistently call the ***heat of reaction*** $\boldsymbol{\Delta H_r}$ and that we depict and define in Figure 6. Of course, when we say *heat of reaction* we mean ***enthalpy change of the reaction***, as indicated by the nomenclature $\boldsymbol{\Delta H_r}$. In Figure 6 we also observe the other necessary conventions, such as expressing $\boldsymbol{\Delta H_r}$ on the basis of ***one mole*** of a selected reactant or product, generally per mole of the product of interest, and that of keeping tabs on the reference state for the reactants and products so the necessary adjustments can be made if our actual reaction yields the compounds at different states (i.e., solid, solution, liquid, vapor, or gas).

Hydrogenation of nitrobenzene to aniline



Depending on whether the reaction is endo- or exothermic, ΔH_r will be >0 or <0, as per Fig. 5. Note, however, that the reference state for each reactant and product is specified reflecting the fact that the value of ΔH_r will be a affected by the state of each reactant and product. For instance, if unlike the above specifications the product stream mass were to yield aniline in the liquid state ***and water as vapor***, the value of ΔH_r would differ, since the overall reaction would spend (or need) an amount of energy for the evaporation of the water (i,e., the latent heat of evaporation of the two moles of water).

For consistency and convenience, the value of ΔH_r is ***always*** expressed in units of energy per g-mole of reactant or product. Thus the ΔH_r as ***Kcal/mole of aniline*** product is ***twice*** the value of the ΔH_r as ***Kcal/mole of water*** product, but maintaining the + or – sign.

In thermochemistry, stoichiometry does matter.

FIGURE 6 The reduction of nitroaromatics, among other reactions, sometimes permits the actual isolation of intermediate products, along the lines of Gibbs transition intermediates.

> Thermodynamic properties and thermochemical data are, by convention, tabulated in their sources at the ***standard reference*** state—atmospheric pressure and 25°C or 298°K.

But how do we obtain the values of ΔH_r, that crucial datum for our ***safe*** approach to running chemical reactions? Let us first go to Dodge's quotation, which teaches that all we need to do is subtract the total enthalpies of the reactants from that of the products, which is simple enough if we follow the conventions (just as an accountant needs to make entries in the proper columns of the ledger and make sure all entries are on the same basis and units, such as being for the same accounts and in the same units of currency). What is not simple is to obtain the enthalpies of the reactants and of the products; and so much of thermochemistry work is based on experimental measurements of heat effects—that is, ***calorimetry***. Nevertheless, for the relatively simple structures for which enthalpy data are available (13), the work is straightforward provided we know what to do with the individual ***H*** values for the reactants and the products. Fortunately, here where we come across and apply ***Hess's Law***, the foundation and the most useful tool of thermochemistry, as we now discuss in Figure 7.

Although the quantitative framework of thermodynamics was not yet assembled during his lifetime, Hess understood that it is only the change between initial and final states of the system that matters (recall the previous quotation from Dodge a century later)—thus his brilliant use of nonexistent reactions to fill blanks in an arbitrary set of reactions that results in the ***net reaction*** from the chosen reactants to the desired products. Hess, once armed

Enthalpy change ΔH_r of a reaction system – Hess Law

The overall heat effect of a chemical reaction is the sum of the heat effect of the chemical steps into which the reaction may be divided, even if the division is strictly theoretical (i.e., the partial reactions need not be known to occur). For example, for the reactions $A \rightarrow B \rightarrow C \rightarrow D$ that take place via a common reactant P (e.g., oxidations with H_2O_2):

Germain Henri Hess
Swiss-Russian (1802–1850)

$$\left.\begin{array}{lllll} A + P & \rightarrow & \cancel{B} + \Delta H_r^{1} & \textit{Exo} \\ \cancel{B} + P & \rightarrow & \cancel{C} + \Delta H_r^{2} & \textit{Endo} \\ \cancel{C} + P & \rightarrow & D + \Delta H_r^{3} & \textit{Exo} \end{array}\right\} \Sigma(\Delta H_r)$$

$$\begin{array}{lllll} A + 3P & \rightarrow & D + \Delta H_r & \textit{Exo} \end{array}$$

Each ΔH_r goes into the sum with its own sign: Exos are – and endos are +.

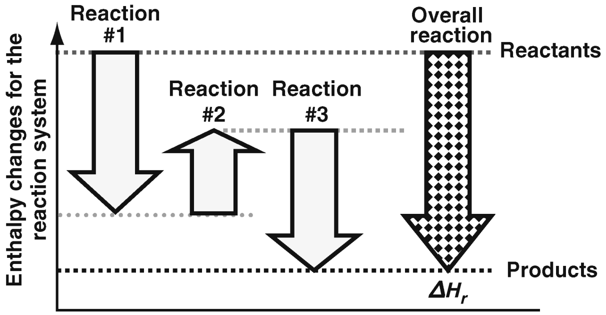


FIGURE 7 Hess's imaginative breakthrough to get from products to reactants and their energy change.

Heat of formation - ΔH_f

To obtain the ΔHr for a given reaction directly – without recourse to component reactions – we need to know the *direct* contribution of each reactant and product molecule to the ΔH_r. Hess came up with another concept – *the heat of formation* ΔH_f – defined as the ΔH_r of a reactant or product molecule obtained by synthesis from the pure constituting elements. The latter were arbitrarily assigned enthalpy values of zero, thus creating a reference state (or a zero baseline) for all such reactions of *formation.*

Armed with the zero baseline, Hess applied his own law to obtain heats of formation ΔH_f, which in turn could be used to obtain the enthalpy changes of reactions (more commonly known as *heats of reaction* ΔH_r) as per Fig. 6. This was a major breakthrough, for the heat released or needed by chemical reactions is a crucial piece of knowledge for safe and sound chemical processing.

Obtaining heats of formation, however, required astute use of Hess law, for many compounds cannot be synthesized directly from pure elements. Let's see how Hess went about obtaining the ΔH_f for crystalline $ZnSO_4$:

Oxidize Zn metal to ZnO	Measured as	–5291	units	exo
Burn S in air to obtain SO_3	Ditto	–6384	“	exo
Dissolve SO_3 in water to dilute H_2SO_4	Ditto	–2566	“	exo
Dissolve ZnO in dilute H_2SO_4	Ditto	–1609	“	exo
		–15850	“	exo
Correction for the exo $\Delta H_{solution}$ of $ZnSO_4$ in water		1193	“	
ΔH_f for *crystalline* $ZnSO_4$		–14657	units	exo

FIGURE 8 A lot of laboratory work went into the foundations of thermochemistry.

with his law, went further and also ***conceived*** a most useful entity for thermochemical calculations—the ***heat of formation*** ΔH_f, described in Figure 8. By conceiving a sound ***zero baseline*** for the enthalpy of ***any*** compound, Hess made it possible to approach the far more important issue of ***heats of reaction*** ΔH_r through the use of the heats of formation as dictated by his own Hess's Law. Thus, we can express Hess's Law in its ***most useful*** application as:

$$\sum n(\Delta H_f)_{\text{products}} - \sum n(\Delta H_f)_{\text{reactants}} = \Delta H_r \tag{10.6}$$

Where n is the stoichiometric coefficient of each compound. This point about observing the stoichiometry of the reaction in the above equation is elaborated in Figure 6 and an example given in Figure 10.

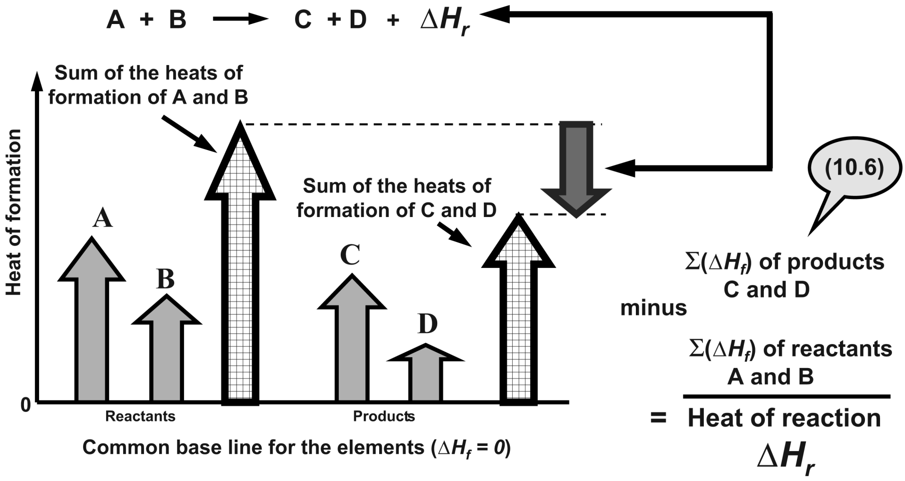
A graphic depiction of this most powerful relationship of thermochemistry is presented in Figure 9. Thus, access to reliable data or estimates of ***heats of formation*** ΔH_f paves the way to the estimation of the more important ***heats of reaction*** ΔH_r, for the latter are not only needed for sound development and design of chemical reaction processes ***but are also a major source of thermochemical hazards***. The use of heats of formation ΔH_f is illustrated further in Figure 10, where we apply the ΔH_f approach to the heat of reaction of our previous reaction example—the hydrogenation of nitrobenzene to aniline.

Nevertheless, and seeing in Figure 8 how much lab work Hess had to carry out to get to the ΔH_f of crystalline $ZnSO_4$, we can readily conclude that for a reaction with even slightly richer organic structures—say, nitrobenzene and aniline in Figure 10—synthesis from the pure elements is rarely possible, and it would take much effort to come up with suitable reactions to sum up as Hess did for $ZnSO_4$—other methods would be useful in estimating ΔH_r.

Determining ΔH_r from the heats of formation ΔH_f

The heat of reaction can be calculated by applying Hess Law on the basis of the heats of formation ΔH_f of the reactants and the products.

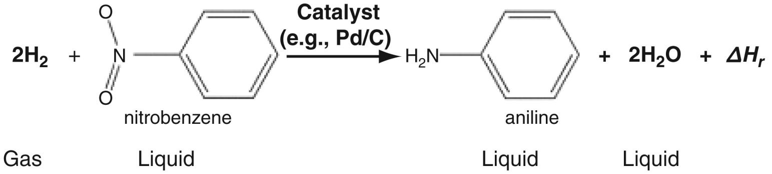
From the common baseline of the elements, for the reaction


A + B ⟶ C + D + ΔHr
Sum of the heats of formation of A and B
Heat of formation
A
B
Sum of the heats of formation of C and D
C
D
0
Reactants
Products
Common base line for the elements (ΔHf = 0)
(10.6)
Σ(ΔHf) of products C and D
minus
Σ(ΔHf) of reactants A and B
= Heat of reaction ΔHr

In this particular instance $\Delta H_r < 0$ ***Exothermic***

FIGURE 9 The concept of heat of formation, also from Hess as an extension of his law, paved the way for the major advances in thermochemistry and remains its most useful tool.

Heats of formation in obtaining ΔH_r


2H2 +
nitrobenzene
Catalyst (e.g., Pd/C)
H2N
aniline
+ 2H2O + ΔHr
Gas
Liquid
Liquid
Liquid

ΔH_f data exist for a good many organic compounds of relatively simple structures, such as the ones in our example reaction above. The following ΔH_f, values are compiled in Stull et al [13] from the standard reference temperature of 25°C/298 °K:

ΔH_f at 25°C/298 °K (*)

Nitrobenzene (liq)	3.8 Kcal/g-mol
Aniline (liq)	7.4 “
Water (liq)	–68.3 “

Applying Hess Law as per Equation 10.6:

$\Sigma(\Delta H_f)$ for the products = (7.4) + (2)(-68.3) = –129.2 Kcal/g-mol

minus

$\Sigma(\Delta H_f)$ for the reactants = (2)(zero) + (3.8) = –3.8 Kcal/g-mol

ΔH_r at 25 °C = **–133.0 Kcal/g-mol of aniline (exo)**

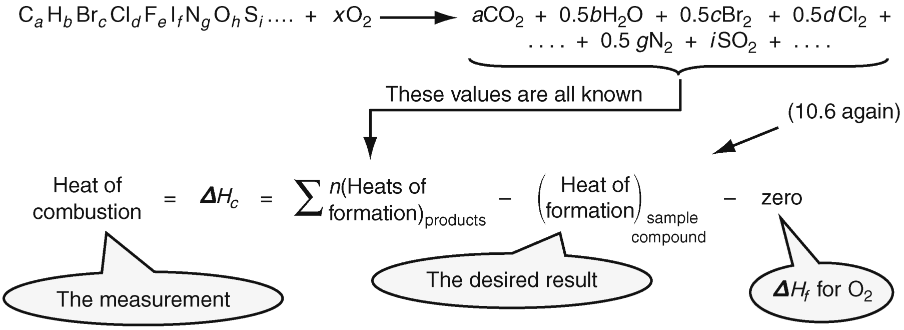
Where ΔH_r is the heat effect of most interest for sound and safe processing

FIGURE 10 Using heats of formation to obtain what interest us most—heats of reaction.

Heat of combustion ΔH_c
Another tool to estimate ΔH_f and ΔH_r

Over a century and a half of largely experimental work a rich database on heats of formation has been accumulated, such as [10]. Alas, we work with many compounds that have complex structures and their experimental determination of ΔH_f from pure elements is not feasible.

Fortunately, Hess Law helps us again, for we can readily obtain the *heat of combustion* ΔH_c for such compounds. Consider a general case where we carry out the *complete* combution (in pure O_2) of a sample compound for which we seek its heat of formation ΔH_f:



$$C_aH_bBr_cCl_dF_eI_fN_gO_hS_i.... + xO_2 \longrightarrow \underbrace{aCO_2 + 0.5bH_2O + 0.5cBr_2 + 0.5dCl_2 + ... + 0.5\,gN_2 + iSO_2 + ...}_{\text{These values are all known}}$$

$$\text{Heat of combustion} = \Delta H_c = \sum n(\text{Heats of formation})_{\text{products}} - \left(\begin{matrix}\text{Heat of}\\ \text{formation}\end{matrix}\right)_{\text{sample compound}} - \text{zero}$$

Note, however, the danger of inaccuracy when summing up large numbers (the heats of combustion) to obtain by difference the often relatively small numbers for the heat of reaction via Equation 10.7.

FIGURE 11 Heats of combustion provide another experimental tool that also exploits Hess's Law. It is, however, subject to large errors ***when the heats of combustion are much larger*** than the heat of reaction we are trying to calculate. Thus, the method must be used with care, and if we use any large heat of combustion (e.g., a hydrocarbon ΔH_c), we should be confident of its accuracy.

For organic compounds that can burn ***completely*** in pure oxygen to ***known*** combustion products, there is a calorimetry tool to obtain the potentially useful ***heat of combustion*** ΔH_c.

> The use of pure oxygen in ample molar excess ensures that the combustion products of C and H are those with known oxidation states (e.g., H_2O, CO_2, and ***not*** a mixture with CO), whereas for the rest we may obtain (depending on the experimental conditions) varying combustion products (e.g., $HCl_{(aq)}$ vs. $Cl_{2(g)}$, SO_2 vs. $H_2SO_{4(aq)}$, N_2 vs. $HNO_{3(aq)}$). If we know the actual products from the combustion calorimeter (Fig. 11), then we have, through one more application of Hess's Law, a path to values of ΔH_f and from there to values of ΔH_r.

Let us carefully consider Figure 11, where we discuss the ***heat of combustion*** ΔH_c and its value in obtaining the real target, that is, the ***heat of formation*** ΔH_f.. Clearly, this gives us a simple calorimetric method for determining the heats of formation ΔH_f of complex organic compounds via equation (**10.6**), as shown in Figure 11. But the value of the measurable heat of combustion ΔH_c may go further, since for a reaction in which the heat of combustion values ΔH_c for all reactants and products are known, we can also obtain the value of ΔH_r by using as the baseline ***not the pure elements*** but the complete combustion products of all reactants and products in the reaction equation:

$$\sum n(\Delta H_c)_{\text{reactants}} - \sum n(\Delta H_f)_{\text{products}} = \Delta H_r \qquad (10.7)$$

Note that the above equation, ***based on heats of combustion*** rather than heats of formation, ***switches the order of the summation terms***, but each quantity within the summation carries its corresponding sign, as always. This switch of the terms of equation (**10.6**) comes about by the fact that if the reaction equation is generated by summing the individual combustion reaction equations, the result of applying equation (**10.6**) results in equation (**10.7**).

> There is, however, a caveat to the use of equation (**10.7**), namely, the usual problem of adding and subtracting the large numbers (i.e., the heats of combustion) to obtain, ***by difference***, a usually smaller number for the heat of reaction. This sometimes severe limitation in the use of experimental heats of combustion to obtain otherwise unattainable heats of formation is discussed in the caption of Figure 11.

In summary, Hess's Law gives us an array of methods that, with the aid of ***calorimetry***, often enough allows us to determine or calculate the all important ***heats of reaction*** ΔH_r, or more rigorously, the reaction enthalpy changes ΔH. As one more example, consider Figure 12, in which we describe how Hess's Law allows us to combine reactions with known heat effects to obtain the unknown ΔH_r of another reaction expression, one that can be legitimately written from the former through the use of Hess's Law.

On the basis of Hess's Law and the recognition that practically all chemical ***reaction*** processing in our context—that of intermediates and bulk drugs—takes place without significant pV work (i.e., mostly constant pressure and modest changes in volume across reaction), we have been able to exploit Hess's Law

Hess Law allows us to combine reactions to get an unknown *ΔH_r*

Hess Law also lets us calculate a heat of reaction by gathering reactions (*with known ΔH_r values*) that may be combined to obtain the reaction of interest. Again, *the pathway between the final and initial states does not matter* to changes in functions that have been defined accordingly (e.g., energy, enthalpy, free energy).

In the example at hand we seek to calculate the ΔH_r of the conversion of CO to CO_2 from the known ΔH_r values for the complete combustion of carbon (Reaction #2) and from that for its partial combustion to CO (Reaction #1), which is also known.

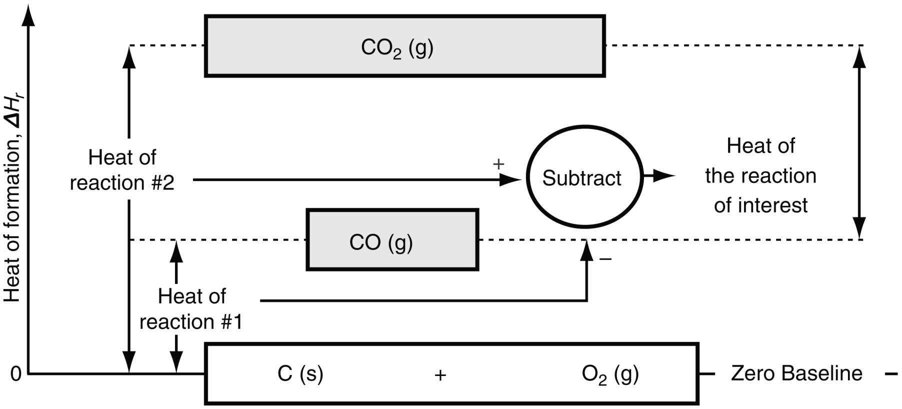


FIGURE 12 One more clever manipulation allowed by Hess's Law—the artful combination of real reactions with known values of ΔH_r. *Abbreviation*: ΔH_r, enthalpy change of the reaction.

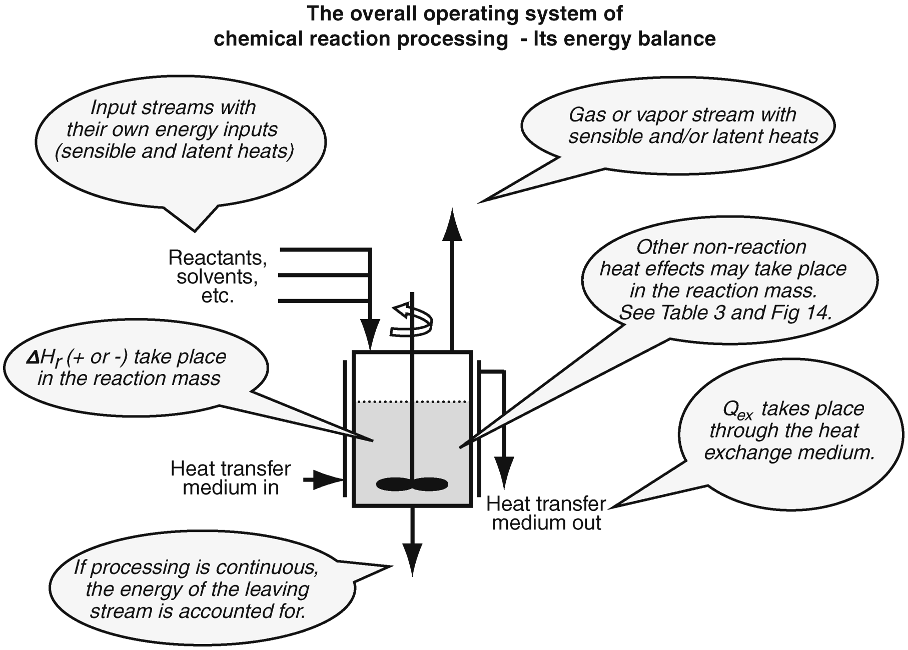

The overall operating system of chemical reaction processing - Its energy balance
Input streams with their own energy inputs (sensible and latent heats)
Gas or vapor stream with sensible and/or latent heats
Reactants, solvents, etc.
Other non-reaction heat effects may take place in the reaction mass. See Table 3 and Fig 14.
ΔHr (+ or -) take place in the reaction mass
Qex takes place through the heat exchange medium.
Heat transfer medium in
Heat transfer medium out
If processing is continuous, the energy of the leaving stream is accounted for.

FIGURE 13 In chemical processing the energy balance is no less important than the mass balance, as well as crucial when thermochemical hazards are at hand.

while concerning ourselves only with the enthalpy changes between initial states (i.e., reactants) and final states (i.e., products) such that ***all thermochemical events result in energy transfer as heat***. Thus the logical focusing of our interest on heats reaction ΔH_r—the source of the energy for thermochemical hazards and risks—and our use of heats of formation and combustion as often helpful tools when combined with the reach of Hess's Law—thus the summary of Table 2, in which we list the principal equations used in thermochemical calculations as they apply to the crucial energy balance in Figure 13 shown above.

B. The Totality of Heat Effects in Chemical Processing

Thermochemistry, ***in skillful combination*** with the proper experimental tools, gives us insights into the energy releases from chemical reactions—their onset conditions and their magnitude—and thus serves as the first line of inquiry in thermochemical hazards assessment. Thermochemistry, however, teaches us nothing about the *rate* of energy releases, for such is the realm of chemical kinetics. Thermodynamics, as the mother lode discipline, is equally impotent. It can teach us about the ***likelihood*** of chemical reactions, their ***equilibria***, and, through its thermochemistry subdiscipline, about their ***heat effects***. Still, thermodynamics cannot teach us about the ***rate*** of reactions.

Yet, in effective and safe chemical processing, we are utterly interested in ***the rate at which thermochemical energy is released***, for such a rate makes the difference between a safe and a hazardous process. Beyond that, the combined

TABLE 2 Working Equations for Our Thermochemical Calculations, as well as for Doing Energy Balances in Reaction Systems

Heat of reaction ΔH_r from the heats of formation ΔH_f of reactants and products.

$$\sum \boldsymbol{n}\,(\Delta \boldsymbol{H}_f)_{\text{products}} - \sum \boldsymbol{n}(\Delta \boldsymbol{H}_f)_{\text{reactants}} = \Delta \boldsymbol{H}_r \tag{10.6}$$

Heat of reaction $\Delta \boldsymbol{H}_r$ from the heats of combustion ΔH_c of reactants and products.

$$\sum \boldsymbol{n}(\Delta \boldsymbol{H}_c)_{\text{reactants}} - \sum \boldsymbol{n}(\Delta \boldsymbol{H}_f)_{\text{products}} = \Delta \boldsymbol{H}_r \tag{10.7}$$

Enthalpy change due to sensible heat gain or loss ΔH_s

$$\Delta \boldsymbol{H}_s = \mathrm{M}\boldsymbol{C_p}(\boldsymbol{T}_{\text{final}} - \boldsymbol{T}_{\text{initial}}) = \mathrm{M}\boldsymbol{C_p}\Delta \boldsymbol{T} \tag{10.8}$$

Enthalpy change due to latent heat of phase changes $\Delta \boldsymbol{H}_l$

$$\Delta \boldsymbol{H}_l = \boldsymbol{ML} \tag{10.9}$$

In working with all of the above equations, attention must be paid to have consistency with the units of energy in all instances (no mixing of kcals, kilojoules and BTUs), as well as work on the basis of moles as the consistent unit of mass and °C or °K as consistent units of temperature.

Abbreviation: BTU, British thermal unit.

magnitude and rate information allows us to make the most basic choices as to how best deal with a thermochemically hazardous process concept:

- Abandon it and seek alternative chemistry or drastically different reaction conditions.
- Take it forward into scale-up with a suitable process design and reassess the risks from the results.
- If a process design choice emerges with acceptable risks, complete the scale-up and the process design at scale for implementation after a successful risk analysis of the process ***as it will be implemented***.

The task, however, is complicated by the fact that, and particularly at scale, we often run chemical reactions simultaneously with heat effects other than those of the reactions proper. Sometimes we choose to do so for sound process reasons, or the accompanying heat effects are inevitable. Altogether, we need to reconcile the magnitude and rates of heats of reaction with whatever else may happen so we can approach ***the totality of heat effects***. Table 3 is our attempt to identify all those other heat effects that we choose to call physicochemical in contrast with those of reactions in which we convert reactants into products. Granted, for the sake of creating a complete table, we have included some unlikely events (e.g., sublimation while running a chemical reaction), but some of the events listed are not only probable but also desirable objectives of our process design (e.g., running a scaled-up Grignard reaction in refluxing THF rather than the conventional cold procedure). Thus we come to Figure 15 as a graphic complement to the comprehensive list of heat effects and to Figure 14 as a specific example of a phase change occurring during reaction with its own significant and consequential heat effect. Thus we are led to the concept of the ***energy balance*** for any chemical processing operation and, most particularly, to the energy balance of a thermochemically hazardous process we might choose to run at an acceptable level of risk. Often enough we do so, as stated earlier, through:

> "…skilled implementation specifics—good process design, safeguards of process control, containment of process streams, and, in the extreme, abatement provisions for materials that might be released from the process upon mishap or, additionally, location of the processing activity far from populated areas."
>
> Perhaps this is a good juncture to urge the reader to review what process design is all about (chap. 2, sect. "The Bulk Drug Process as Part of the Drug Development Program"), for it is the activity through which we safely implement a thermochemically hazardous process or operation (i.e., at an acceptable level of risk).

Just as process design cannot take place without material balances, the corresponding energy balances are just as indispensable. Whenever a release of thermochemical energy is expected and especially if a thermochemical hazard has been identified, the energy balance is crucial to ensure that the process design and operation proceed as intended, and the balance needs to integrate all heat effects that may accompany the chemical reaction processing at hand. This was first suggested in Figure 13 and is now elaborated in Figure 15, culminating in the determination of the rate and extent that thermal energy may ***accumulate*** in the process through its intended operation *or* ***by mishap***. In general, it is a

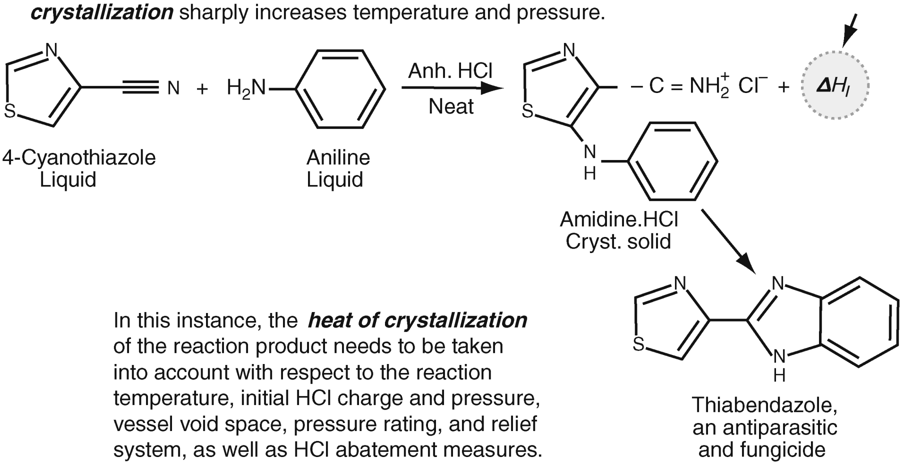
TABLE 3 Physicochemical Heat Effects That May Accompany a Chemical Reaction

There are numerous physicochemical events that, although not necessarily involving a chemical reaction, have their own heat effects and often take place during the reaction processing. Their heat effects not only need to be included in the complete energy balance of the reaction system, but they must also be integrated in the scale-up and process design, sometimes advantageously.

Nonreaction event	***Nature of the event***
Adsorption	Gas phase component adsorbs onto a solid surface. Solute in a liquid adsorbs onto a solid surface.
Absorption	Gas phase component absorbs into a liquid.
Chemisorption	This is a special case of adsorption in which binding is stronger.
Condensation	Vapor component becomes a liquid. Vapor component directly becomes a solid—opposite of sublimation.
Crystallization	Solute in a molten or solution liquid phase incorporates into a crystalline solid.
Solvation	Solute in a molten or solution liquid phase incorporates into a crystalline solid.
Desorption	Adsorbed component leaves the solid—reverse of adsorption.
Dilution	Solution plus solvent result in a more dilute solution.
Fusion	Solid phase becomes a liquid phase (i.e., melting).
Freezing	Molten liquid becomes a solid phase, not always crystalline.
Evaporation	Component(s) of a liquid phase become(s) a vapor.
Mixing	Pure liquids are blended to form a homogeneous liquid mixture.
Solution	Solid phase dissolves into a liquid phase.
Stripping	Gas removes a component from a liquid—reverse of absorption.
Sublimation	Solid phase becomes a vapor directly.
Reaction events	
Combustion	Any compound reacting with oxygen to various products of oxidation, generally gaseous
Dissociation	Compound into ions, usually in a solution and often in ionic equilibrium
Formation	Pure elements converted to a pure compound
Reactions at large	Reactants to products, rarely without accompanying or consecutive "side" reactions

Physicochemical heat effects acompanying chemical reaction

The reaction that yields the amidine intermediate to thiabendazole is accompanied, upon reaching high conversion, by very rapid and highly exothermic crystallization of the amidine.HCl. As the reaction is run under anhydrous HCl, the large latent exo ***heat of crystallization*** sharply increases temperature and pressure.

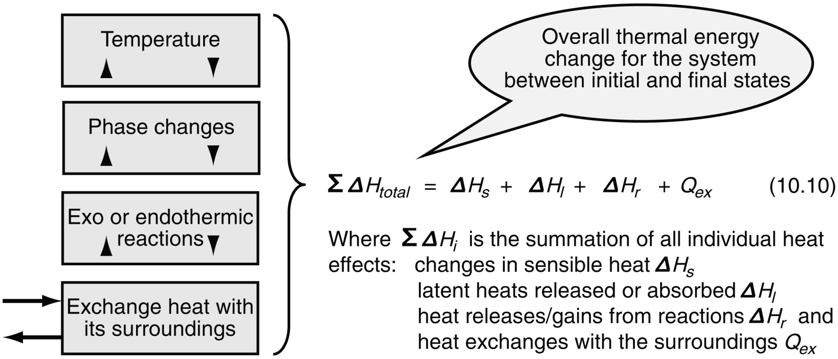

N
S
N + H_2N
Anh. HCl
Neat
N
S
$- C = NH_2^+\ Cl^-$ +
ΔH_l
N
H
4-Cyanothiazole
Liquid
Aniline
Liquid
Amidine.HCl
Cryst. solid
N
N
S
N
H
Thiabendazole,
an antiparasitic
and fungicide

In this instance, the ***heat of crystallization*** of the reaction product needs to be taken into account with respect to the reaction temperature, initial HCl charge and pressure, vessel void space, pressure rating, and relief system, as well as HCl abatement measures.

FIGURE 14 Not all heat effects of importance to the energy balance are thermochemical.

The overall energy balance

In our context of chemical processing (i.e., no work done by or on the system), we depend on the following equations and those for the individual heat effects (as per text and Table 2).


Temperature
▲ ▼
Phase changes
▲ ▼
Exo or endothermic
▲ reactions ▼
Exchange heat with
its surroundings
Overall thermal energy
change for the system
between initial and final states

$$\Sigma\, \Delta H_{total} = \Delta H_s + \Delta H_l + \Delta H_r + Q_{ex} \qquad (10.10)$$

Where $\Sigma\, \Delta H_i$ is the summation of all individual heat effects: changes in sensible heat ΔH_s
latent heats released or absorbed ΔH_l
heat releases/gains from reactions ΔH_r and
heat exchanges with the surroundings Q_{ex}

If the system is open (i.e., mass exchanges with the surroundings). the energy balance equation must include the energy contributions of inputs and outputs:

$$\Sigma(H \text{ of inputs}) + \Sigma(\Delta H_{total}) + \Sigma Q_{ex} - \Sigma(H \text{ of outputs}) = \boxed{\text{Accumulation of thermal energy* in the system}} \qquad (10.11A)$$

***In the event of depletion, the accumulation term is negative**.

FIGURE 15 The accumulation of energy in a chemical reaction system is the bottom line of energy balance.

cardinal rule of thermochemical process safety to limit such accumulations to instances in which they

a. are not accidental (i.e., they are part and parcel of the intended course of events, such as using heat of reaction to reach a desired operating temperature and pressure) and
b. are well controlled and within the desired margin of safety (e.g., our cooling capacity amply exceeds the foreseeable rate of accumulation).

In determining the accumulation rate of energy in reaction processing, we need, as shown in Figure 15, to include the heat effects accounted by temperature changes in the process mass (equation **10.8**) and by phase changes, such as evaporation or crystallization (equation **10.9**):

$$\begin{aligned} \boldsymbol{\Delta H}_{\mathrm{s}} &= \textbf{Enthalpy change due to sensible heat gain or loss} \\ \boldsymbol{\Delta H}_{\mathrm{s}} &= (\textbf{Mass})(\textbf{Heat capacity})(\textbf{Temperature change}) \\ &= \boldsymbol{MC_p}(\boldsymbol{T}_{\textbf{final}} - \boldsymbol{T}_{\textbf{initial}}) \\ \boldsymbol{\Delta H}_{\mathrm{s}} &= \boldsymbol{MC_p \Delta T} \end{aligned} \tag{10.8}$$

and

$$\begin{aligned} \boldsymbol{\Delta H}_{\mathrm{l}} &= \textbf{Enthalpy change due to the } \textbf{\textit{latent}} \textbf{ heat released or} \\ &\qquad \textbf{absorbed by phase change} \\ \boldsymbol{\Delta H}_{\mathrm{l}} &= (\textbf{Mass})(\textbf{Latent heat of the phase change}) = \boldsymbol{ML} \end{aligned} \tag{10.9}$$

For a reaction system that is continuous—steady input and output streams—we need to account for the ***sensible*** and ***latent*** energy content of inputs and outputs, as shown in Figure 15. Finally with respect to the energy balance of a chemical reaction system and Figure 15, all of the above is, of course, based on a baseline reference temperature, most conveniently the lower of T_{initial} or T_{final}.

C. Calorimetry

Calorimetry is based on a broad array of methods for the measurement of energy as it is released (or absorbed) as heat by various phenomena. Conversely, it is also used to quantitatively study the behavior of materials as heat is transmitted to them in known amounts and under known conditions, such as rate of temperature increase or some particular atmosphere. Both techniques are used in the assessment of thermochemical hazards. Table 4 is an attempt to most briefly describe these methods and place them into their proper application pigeonholes. The list of methods that can be found in the literature is longer [(4), pp. 35–45], but the development and wide utility of the relatively new ***process calorimeter*** seems to render some older calorimetry methods obsolete—thus our limited list that follows.

> The word ***calorimetry*** derives from ***calor*** (Latin for warmth, heat, passion, etc.) and ***metron*** (Greek for measure). Understanding heat was long in coming, even if as early as the 17th century prescient views of heat as conceptually related to ***activity*** and ***motion*** had been expressed by Francis Bacon, to whom the essence of heat was motion, and by Robert Hooke (Isaac Newton's nemesis), for whom heat was the result of the "brisk and vehement agitation" of particles in a mass. Yet, the vague

TABLE 4 The Calorimetry Tools of Hazards Assessment

Conventional calorimeter and variations thereof—Fig. 16	Measurement of heat effects upon bringing two or more materials (or process streams) together. Suitable for $\Delta \boldsymbol{H}_r$ of relatively fast single reactions, heats of dilution
Combustion calorimeter—Fig. 16	Measurement of $\Delta \boldsymbol{H}_c$ that may be then be used to get $\Delta \boldsymbol{H}_f$ of complex organic compounds
Process calorimeter—Fig. 17A	Totality of heat effects along the course of batch or semibatch process operations (not just reactions) under scaled-down conditions approaching actual processing sequence of events; reasonably capable of discriminating among many of the heat effects, estimation of rates, and heat balances
ARC—Fig. 18	Measurement of onset and magnitude of heat effects that elude all other methods—for example, slow and low temperature onset "self-heating" reactions
DSC—Figs. 19 and 20	Sensitive and first tool to ***screen*** for heat effects and their quantification, but incapable of approaching actual processing conditions; also useful for postscreen follow-up that may lead to larger sample work or ARC
Pilot-scale energy balances	Scaled-up version of process calorimetry; requires heavily instrumented equipment with computer control and algorithm execution, data analysis, etc.

An assortment of complementary, ***non-calorimetric*** tools exists to ferret out and measure all the variety of thermochemical hazards. Such tools will be discussed elsewhere in this chapter.
Abbreviations: ACR, accelerating rate calorimetry; DSC, differential scanning calorimetry.

notion of heat as some sort of peculiar fluid substance persisted, and indeed it was Lavoisier, "the father of chemistry," who in 1789, a few years before losing his head at the guillotine during the French Revolution, advanced the "caloric" hypothesis by listing such "substance" as the first, with light as the second, in his list of the 33 elements as per his reckoning at the time. Not until Rumford, experimenting while fabricating brass cannons for the Duke of Bavaria in 1799, proved that heat could not be a substance, for it came out inexhaustibly as he bored repeatedly into cylindrical brass castings (8). Alas, reliable measurements of heat in the ingenious but bulky apparatus of Rumford were not possible, and it was left to Joule to make such measurements with much experimental finesse (Fig. 4).

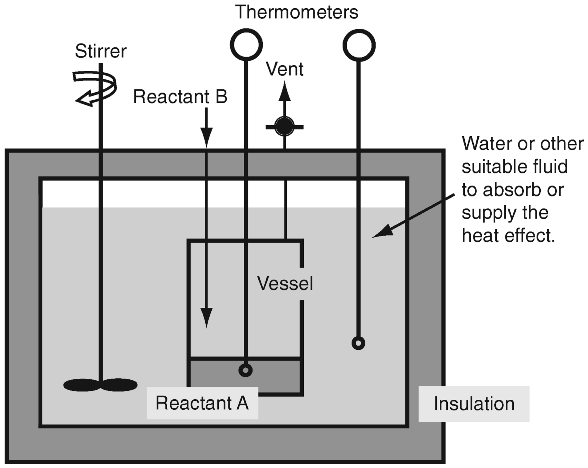
1. The Conventional and the Combustion Calorimeters

As shown in Figure 16, the conventional calorimeter measures the heat output of the phenomenon under study (e.g., a chemical reaction, a crystallization, a dilution) by rapidly bringing together sufficient amounts of reactants or components and measure the temperature change to the final thermal equilibrium condition. In applying equation (**10.8**) both the mass of surrounding fluid and that of the vessel and its contents are taken into account, as well as any corrections from calibration work on the apparatus. For the measurement of heats of combustion, the vessel is suitable for vacuum and pressure operation, as well as fitted with an electric ignition device and a port for admitting pure oxygen.

The limitation of the conventional apparatus is twofold: (a) the mixing of the reactants or components is rather haphazard, which in the case of multiple reactions may grossly alter the distribution of the products, and (b) other events, either simultaneous (e.g., refluxing) or subsequent to the chemical reactions (e.g., work-up manipulations) cannot be carried to measure their heat effects. Actually, the conventional calorimeter is only well suited for measuring heat

Calorimetry
The original calorimeter and variations thereof

The apparatus is shown at its simplest, very much like Joule's (Fig. 4). After calibration and upon mixing of the reactants (or streams) the resulting heat effect is observed as an increase or decrease in the temperature of the surrounding water bath. Equation 10.8 is used to calculate the magnitude of the heat effect based on the mass of water (or other fluid), its heat capacity, the observed ΔT and the corrections called for by the calibration work.


Thermometers
Stirrer
Vent
Reactant B
Water or other suitable fluid to absorb or supply the heat effect.
Vessel
Reactant A
Insulation

Variations on this basic apparatus include those for measuring heats of combustion under pure O_2 with an electric ignition source inserted in the reaction vessel.

Flow versions of the apparatus have been used when the initial mixing of the reactants is an issue (e.g., insulated tubular vessels with multiple T sensors along the length of the tube to obtain the adiabatic ΔT of fast reactions).

FIGURE 16 The basic calorimeter for simple reactions under static conditions.

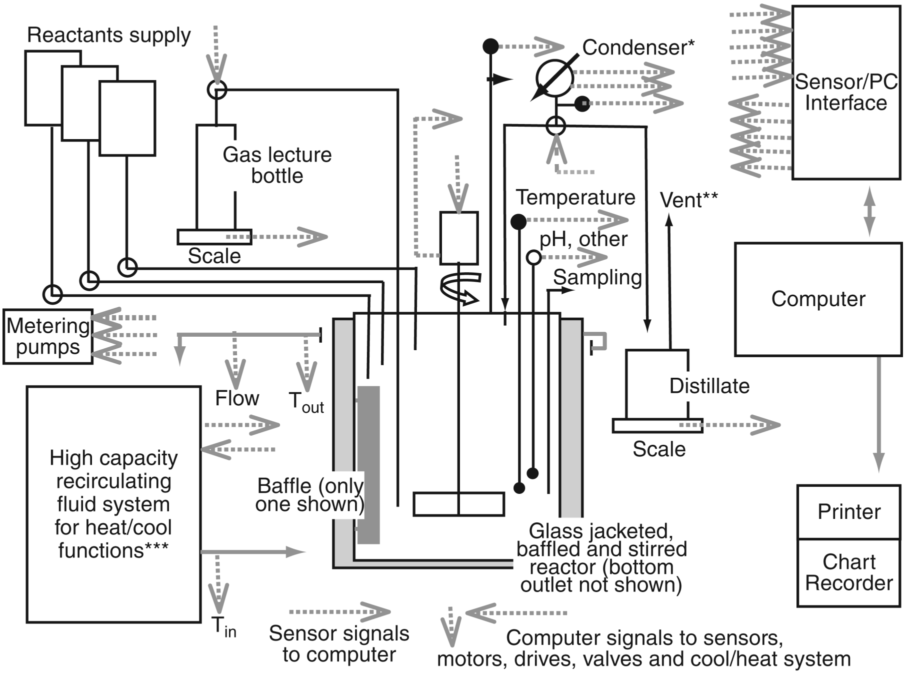
effects of straightforward events—single-phase reactions insensitive to mixing, dilutions, crystallizations via changes in pH or solution phase composition and the like. An ***adiabatic*** calorimeter variation—so called because the heat exchange with the surroundings of the vessel is minimal—measures the heat effect through the ΔT of the reaction mass upon mixing of the reactants and equation (**10.8**) but requires not only calibration of the apparatus for its heat absorption baseline (usually a Dewar flask) but also an additional determination of the heat capacity of the process mass in order to solve equation (**10.8**).

> Adiabatic behavior (from the Greek words for "not passing through") is difficult to obtain in small-scale vessels, where the external surface area is large relative to the amount of process mass within. Nevertheless, the Dewar flask (so named after James Dewar, its creator) insulates its contents rather well—thus its use to hold liquid nitrogen, acetone/dry ice baths, and materials that we wish to keep from exchanging heat with their surroundings. The method of the glass Dewar flask (a vessel jacket evacuated to extremely low pressures and rendered highly reflective by a layer of silver metal deposited on the inner walls of the jacket) has been adopted for a variety of lab apparatus (e.g., distillation, reflux), and some such devices are shown in Figure 17B.

2. The Process Calorimeter

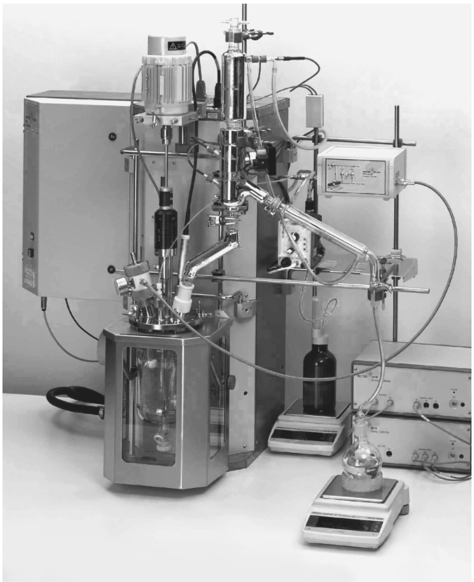
Since chemical processing is seldom so straightforward and simple that it could be run in the conventional calorimeter, more recently a laboratory-scale tool has

Process Calorimeter for batch and semi-batch processing


Reactants supply
Gas lecture bottle
Scale
Metering pumps
Condenser*
Sensor/PC Interface
Temperature
pH, other
Sampling
Vent**
Computer
Flow
T_{out}
Distillate
Scale
High capacity recirculating fluid system for heat/cool functions***
Baffle (only one shown)
Glass jacketed, baffled and stirred reactor (bottom outlet not shown)
Printer
Chart Recorder
T_{in}
Sensor signals to computer
Computer signals to sensors, motors, drives, valves and cool/heat system

(A)

An actual process calorimeter



(B)

been developed that conducts a continuous energy balance under far more realistic processing conditions for not only the chemical reactions at play but also a good many work-up manipulations that might follow. When, as shown in Figures 17A and 17B, the process calorimeter (sometimes called the heat flow calorimeter) is fitted with the proper instrumentation, a capable computer interfaced with the instruments and the appropriate software, the heat effects in the process mass can be measured as they take place in most batch or semi-batch-processing sequences. The use of glass allows for observation of the process mass throughout; the rates at which the heat effects occur can be tracked and the sequence of events in the process under study can be simulated under conditions that, while not avoiding scale-up work, certainly prevent many surprises. These features are most important when the process under study includes thermochemical hazards, such as fast exothermic reactions, consequential changes in phase composition (e.g., the crystallization described in Figure 14), or drastic changes in the heat transfer rate as the reaction mass changes. Additionally, if fitted with larger feed tanks and a bottom outlet for controlled pump-out, the operation of a continuous stirred tank reactor (CSTR) may be also be simulated while continuously carrying out the energy balance. Although the energy balance reflects the ***lumped*** heat effects as they occur, a parallel energy balance on the condenser may be carried out to segregate the latent heat of evaporation ΔH_l that may accompany the heat of reaction. If the chemical reactions occur without accompanying phase changes, then, of course, the energy balance provides the heat of reaction ΔH_r, the temperature change of the reaction mass provides the sensible heat effect ΔH_s, and the energy balance for the recirculating heat exchange fluid (via equation **10.8**) provides Q_{ex}—all the terms needed for the energy balance equation (**10.10**), defined in Figure 15. Even if reactions and phase changes ***other than evaporation*** occur simultaneously (e.g., Fig. 14), we still can solve equation (**10.10**) except that we may not be able to discriminate between the values of ΔH_r and ΔH_l. In all cases, however, we are able to obtain the crucial ***energy accumulation of the process mass*** as a function of time—that is, the rate of energy accumulation that, if positive (as with exothermic reactions), we must provide for by way of cooling capacity and other safeguards against a ***runaway event***, as we will discuss soon enough.

> In our context of thermochemical process safety, a ***runaway event*** is defined by the energy accumulation in a process mass ***exceeding our capacity to deal with it***—we cannot cool, quench, dilute, or evaporate it fast enough—and the temperature increases out of control (i.e., ***runs away***) with whatever consequences attach [pressure increases until it is relieved by the relief system (e.g., Seveso), vessel failure (perhaps explosively), with release of materials and the secondary risks of fire, explosion, environmental contamination, property damage, and possibly injury or death to people and animals (e.g., Seveso, Bhopal)].

FIGURE 17 (**A**) The process calorimeter, a relatively recent development, permits the measurement of heat effects under dynamic conditions that can approximate the total sequence of process manipulations. (*) A subset of the overall energy balance is the energy balance on the condenser at either reflux or distillation conditions. (**) Measurement and collection of any off-gas by-product can be incorporated to the process calorimeter. (***) The well-controlled and high-capacity heat/cool unit permits reliable measurement of the jacket Q_{ex} term of the energy balance as the reaction and other manipulations are executed under temperature control. (**B**) The RC-1e process calorimeter and ancillary equipment. *Source*: Courtesy of Mettler-Toledo Autochem, Inc.

Finally, the process calorimeter teaches a great deal about the ***heat transfer characteristics*** of the process mass through the ***overall heat transfer*** across a heat exchange surface area (i.e., the wetted area of a jacketed stirred tank):

$$\mathbf{Q_{ex}} = (\textbf{A heat transfer coefficient})(\textbf{The heat exchange area})\,(\boldsymbol{\Delta T})$$

Where ΔT **is** the temperature difference between the process mass and the temperature of the medium or exchange fluid ***on the other side of the wall*** that defines the heat transfer surface area:

$$\boldsymbol{\Delta T} = (\boldsymbol{T}_{\mathbf{process}} - \boldsymbol{T}_{\mathbf{exchange\ fluid}}) \tag{10.10}$$

Which in the context of the above equation we call ΔT, ***the driving force for all heat transfer other than by radiation***. Thus we come to the working equation (**10.11**) for the rate of heat transfer $\boldsymbol{Q}_{\mathbf{ex}}$ across the surface area between a process mass and the temperature on the other side of the surface area available for heat exchange:

$$\mathbf{Q_{ex}} = \boldsymbol{UA\,\Delta T} \tag{10.11}$$

We will defer further discussion of equation (**10.11**) for a while, but let us further define **U**, the characteristic proportionality factor—***please note that we refrain from calling it a constant***. Thus, **U** reflects the conditions on ***both sides of the surface***, as well as the properties of the wall that constitutes the surface proper (e.g., the inner cylindrical wall of a jacketed vessel), which explains U being known as the ***overall*** heat transfer coefficient.

> For example, a slowly stirred and viscous process mass, surrounded by a glass enameled steel wall with a rather slow flow of cooler ***oil*** on the other side, will give a **U** much smaller than a well-stirred, low-viscosity process mass surrounded by a plain steel wall with a fast flow of equally cooler ***water*** on the other side.

A straightforward ***units check*** on equation (**10.11**) (a must do ***sanity check*** when working with relatively unfamiliar equations) tells us that *U* is expressed in units as follows:

$$\boldsymbol{U} = (\boldsymbol{energy})/(\boldsymbol{time})(\boldsymbol{surface\ area})(\boldsymbol{\Delta T}) \tag{10.12}$$

Where equation (**10.12**) is merely a rearrangement of equation (**10.11**). In the almost obsolete English system with which the author grew up:

$$\boldsymbol{U} = \mathbf{BTU}/(\mathbf{hr})(\mathbf{ft}^2)(^0\mathrm{F})$$

At this point the reader is challenged to figure out the units of ***U*** in the SI system (i.e., metric). A clue follows: the usual unit of energy is the kilojoule, but sometimes the literature abbreviates by using units of power (e.g., watts) in place of (energy/time).

Finally on the process calorimeter, the reader is also urged to carefully examine Figure 17A. By now the process calorimeter is well established as an indispensable tool in the development of processes, particularly those with thermochemical hazards, as well as a useful ***preliminary basis*** for scaling up such processes into larger stirred tanks, certainly far better than the usual round-bottom flasks in the chemistry bench or the 22 L equivalent in the kilo lab. Nevertheless, the principal values of the process calorimeter are the heat effects data, the energy balance of the process sequence as a whole, and the correlation of the heat effects with observable events, such as phase changes, changes in process mass viscosity, foam development, evaporation, stirring power demands, etc. Again, Figures 17A and 17B describe the process calorimeter tool in some detail, with Figure 17B showing an actual process calorimeter.

3. The Accelerating Rate Calorimeter

The accelerating rate calorimeter (ARC) is a very valuable tool to ferret out those insidious exothermic reactions that, by virtue of being slow at their onset, can be missed by most screening methods—usually by getting lumped with the intended reaction exotherm that has a higher onset temperature. Consider, for instance, the ***actual*** case of an exothermic reaction run relatively cold (~15°C), with sulfur dichloride as the chlorinating agent. As in Seveso, the industrial scale batch was stopped before completion on Friday evening—in this case because of a mechanical mishap downstream. The batch was cooled to –5°C and left at rest (no stirring, no cooling) until Monday morning, by which time the downstream problem would have been fixed. As far as it was known at the time, this was a safe shutdown condition, for the exothermic chlorination was either over or stopped cold, and the well-insulated vessel would not warm up anywhere near renewed chlorination (at least 15°C). Yet, on Sunday morning the unattended batch erupted violently, with a minor vent release, but loosening up the "belly flange" of the glass-lined vessel (the flange closure between the cylindrical vessel and its circular dome cover) and spilling the reaction mass, although without injuries or other serious damage. Unknown to all concerned was the fact that—even at the cold shutdown temperature—exothermic behavior occurred and, in the absence of cooling (plus a very modest heat gain from the warmer surroundings), the reaction mass was by no means dormant but active with slow exothermic activity, ***accumulating energy*** (i.e., getting warmer as the released $\Delta \boldsymbol{H}_r$ turned into $\Delta \boldsymbol{H}_s$), with the unavoidable increase in the rate of whatever reaction(s) took place and further increase in batch temperature until the reaction mass got hot enough—the proverbial ***exponential increase***—to evaporate its solvent and rapidly increase pressure, overwhelming the relief-venting device and prying open the vessel belly flange.

> Careful review of the original thermochemical hazard assessment showed that such a slow exotherm at that lower temperature would not have been revealed, prompting the conduct of more sensitive tests, such as ARC. In the latter, a small sample of the process mass at issue is placed in a pressure capable vessel and subjected to stepwise temperature increases, each followed by a period of "adiabatic wait," namely, the sensitive instrumentation and heat sources maintain the test chamber at the same temperature as the sample between stepwise increases (i.e., no energy gain or loss—thus the term "adiabatic"). If after an arbitrary time interval the sample has not shown a self-heating response, the temperature is increased another ΔT and the system goes back to the adiabatic wait condition, as depicted in Figure 18. This cycle of temperature increases followed by adiabatic waits is repeated until a response is observed or a sufficiently "safe" high temperature is reached without exothermic response. In summary, ARC is the tool of choice for the detection of those slow, low onset temperature exotherms that elude normal screening but that can, over time and in the absence of cooling, "self-heat" with a range of consequences (14).

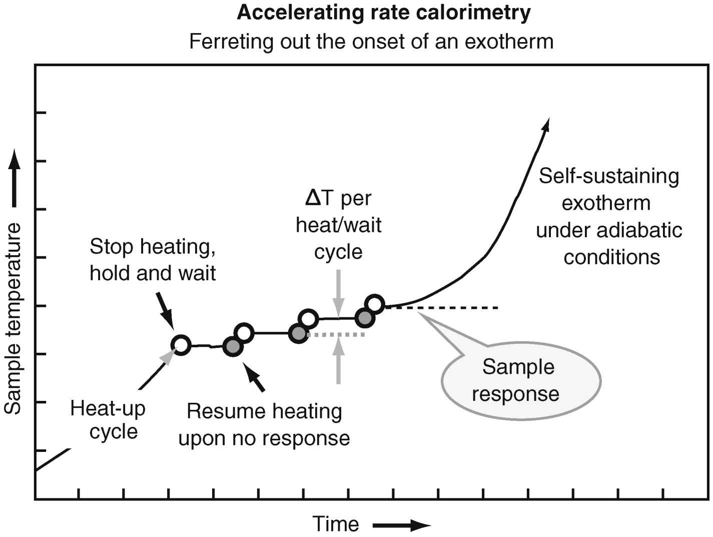

Accelerating rate calorimetry
Ferreting out the onset of an exotherm
Sample temperature
Time
Stop heating, hold and wait
ΔT per heat/wait cycle
Self-sustaining exotherm under adiabatic conditions
Heat-up cycle
Resume heating upon no response
Sample response

FIGURE 18 The ARC seeks slow but potentially hazardous self-heating events. *Abbreviation*: ARC, accelerating rate calorimeter.

Not surprisingly, slow self-heating process masses often arise from aberrant operating conditions, such as those from process interruptions, as well illustrated by the two examples of abnormal Friday night shutdowns in plants operating on five-day-per-week schedules. Indeed, ***some*** such incidents have been found to include ***induction periods*** before the exothermic reaction takes off, sometimes at very fast rates and with eventual explosive behavior. This fact suggests that when the ARC method reveals significant self-heating behavior, the adiabatic wait period should be ***lengthened*** at temperatures below the previously measured threshold of self-heating behavior, thus determining if an induction period exists that would: (a) impose severe limits on any hold times due to processing abnormalities and (b) mandate that the process mass be ***cooled*** if the process sequence is interrupted longer than very briefly.

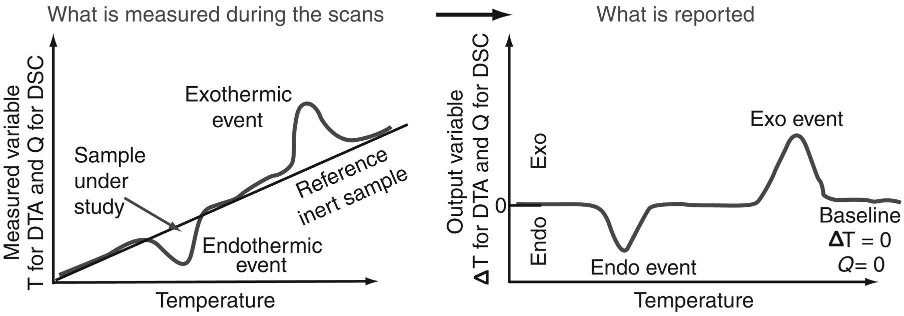
A good illustrative example of the above—the explosion of ~1500 gal of molten 3-methyl-4-nitrophenol *awaiting* final purification at up to 155°C—has been reported (15,16), with subsequent investigation showing a definite induction period under adiabatic conditions (at a much larger test scale than the later ARC method). Thus, holding representative samples of the said process mass gave the following results (16):

a. Holding at 145°C showed no exotherm up to ~160 hours.
b. Holding at 165°C showed very slow self-heating over ***45 hours*** and then a ***sudden*** exotherm to ~520°C.
c. Holding at 185°C gave a somewhat faster self-heating over ***16 hours*** and then a sudden exotherm to ~590°C.

All of which points to an ***induction period*** before the process mass becomes exothermic and the need for further inquiry (e.g., at lower temperatures and longer adiabatic waits) whenever significant exothermic behavior is found in the ARC test.

Differential thermal analysis methods - DTA and DSC

These methods measure the difference of thermal behavior between the sample and an inert reference material. Sensitive mechanisms, instruments and computational attachments permit the study of the thermal behavior of very small samples (typically 5-20 mg) across a modest range of pressure and environmental conditions. Samples under study ***and*** the inert reference are subjected to a programmed increase in temperature, with the inert merely getting warmer and the sample undergoing its various heat effects. The latter (if any exist) provide measurable difference in the thermal behavior of the sample relative to the inert reference. Please see the figures below.



DTA (Differential Thermal Analysis) measures the **ΔT** between the sample and the inert reference as the temperature of the sample is increased at a programmable rate. A hotter sample reveals an exothermic event, whereas a cooler sample reveals an endothermic event. The other trace on the right side shows the reported outputs from the measurements above.

DSC (Differential Scanning Calorimetry) measures the heat flux **Q** needed to maintain the sample at the same temperature as the inert reference. As both sample and reference are heated, greater heat flux to the sample indicates an endothermic event, but less heat flux into the sample means an exothermic event is taking place. The trace above shows the output **ΔT** if DTA and ***Q*** if DSC, relative to a zero baseline in both cases...

FIGURE 19 DSC is the basic tool in first pass screening for thermal hazards. It has many other applications useful in process development.

4. Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) is currently the first-line experimental screening method for the thermal energy behavior of all manner of materials and phenomena. Let us turn to Figure 19 for a description of the DSC operating principles as they derived from the earlier ***differential thermal analysis*** (DTA) method, which was used for thermochemical hazards assessment in a rather qualitative way—it informed about the temperature rise of the exotherm in a given set of test specifics, and it could rank different exothermic events by the magnitude of the temperature rises but could not provide a number for the magnitude of the all important ***energy*** release. Eventually, however, the DTA method evolved into measurement of the ***heat exchange rate (i.e., heat flux) difference*** between that to or from the sample under study and that to or from the *inert* reference sample as the temperature of both sample and reference are increased at a programmable rate—thus the term "differential ***scanning*** calorimetry." The heat exchange rate to or from the ***known sample mass*** under study is measured as units of:

> ***(Heat exchange rate)/(Mass of sample)*** as the temperature of both the sample and the reference is increased at a set scanning rate—the ***known constant rate of temperature increase***—which permits integration of the ***area under the curve*** (AUC in Fig. 19) in units of:

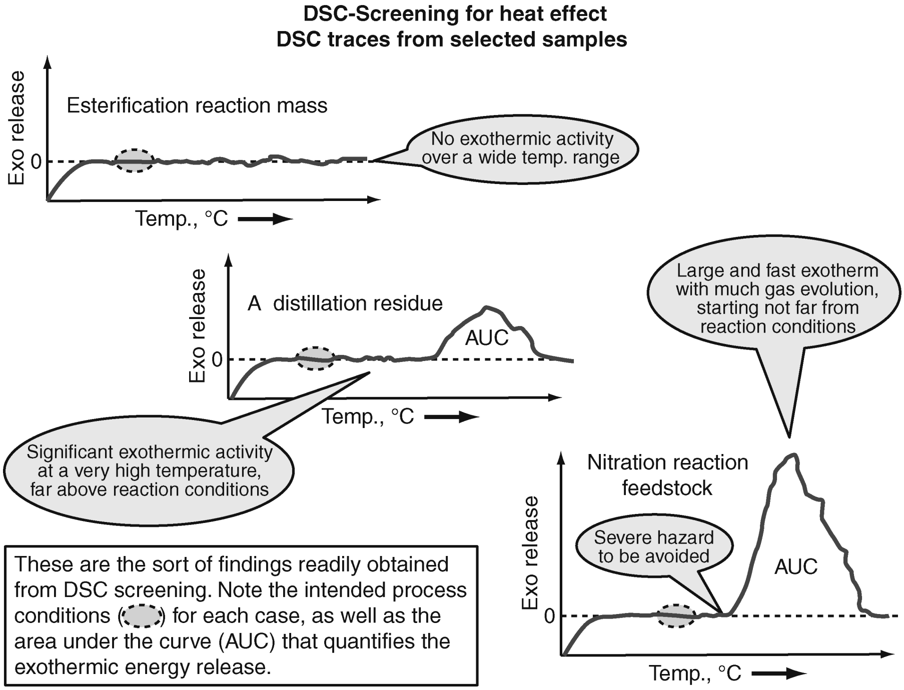


FIGURE 20 Sample DSC traces that reassure us (on the upper left) or that alert us to thermochemical hazard (on the lower right). Note that the distance on the temperature coordinate that separates the processing conditions from the thermochemical event and the magnitude of the latter are the key hazard observations. *Abbreviation*: DSC, differential scanning calorimetry.

$$\mathbf{AUC = (Heat\ exchange\ rate/mass)(Temperature\ interval)}$$

But we can equate a (temperature interval) to a (time interval) through the ***constant scanning rate***, which allows to integrate the AUC in units of:

$$\mathbf{AUC = (Energy)/(time)(mass) \times (Time\ interval\ in\ units\ of\ time)}$$
$$\mathbf{AUC = (Energy/(mass)} \tag{10.13}$$

Thus we obtain the energy release per unit of sample mass for the heat effect that brought about the AUC of the experimental DSC trace. This quantity, of course, is crucial to estimate what the accumulation of energy might be in the energy balance (equation **10.10**) in Figure 15 of a chemical reaction system. Please refer to Figure 20 for an illustration of how the DSC method informs us about the above quantity, and although not quantitatively, it also provides a sense of the rate at which the energy is released, as noted on the DSC trace on the lower right corner of the figure.

The advantages of DSC as a screening tool are several: (a) small samples are required, (b) qualitative and quantitative results are obtained rapidly (say, up to an hour for a full scan), and (c) a wide temperature range can be studied, up to several hundred °C. There are limitations as well: (a) the sample is static, unlike a process mass would be, (b) feasible atmospheres over the sample are limited, and (c) the method requires a reasonably experienced operator to ensure reliable results and interpretation. For example, the scanning rate, if too fast, can distort the trace so as to hide the real onset temperature of an exotherm. As we will discuss in closing the chapter, the tools of thermal hazard assessment are not merely analytical methods; they must be used within a knowledgeable and multidisciplinary process context.

> Although of limited use in thermochemical hazard assessment, there is also thermo***gravimetric*** analysis (TGA), in which the output is the change in the weight of the sample as the temperature scan takes place. TGA is well suited to study phase changes such as evaporation, sublimation, formation of gaseous products, loss of solvation from solids, etc., just as DSC can be used to study phase changes by means of their heat effects. Occasionally, TGA is used to complement DSC and other methods to better understand a hazardous heat effect involving phase changes with loss of mass (e.g., decomposition reactions).

5. Other Methods for Measurement of Thermochemical Heat Effects

Very fast reactions with significant heat effects often need to be run continuously lest their desired distribution of products be grossly distorted by competitive ***consecutive*** reactions. Indeed, such very fast reactions involve mixing of the reactants as a factor in determining product distribution. Since neither the conventional nor the process calorimeter is suitable for those reactions (mixing is not fast enough to avoid the said distortion), a reasonable approach is to study the reaction(s) in an ***adiabatic flow reactor***, as depicted by the ***top*** diagram in Figure 21. Namely, the reactants streams are brought together in the most effective manner we can at the lab scale, and the "well mixed" combined stream fed to a ***well-insulated*** flow reactor (i.e., approaching adiabatic behavior) and the temperature increase of the process stream measured at various points (and at a fast flow rate to achieve ***turbulence***), as illustrated in Figure 21. Such experiments provide ***lumped thermochemical data*** suitable for scaling up without surprises, even if we might not be able to obtain accurate values for the $\Delta \boldsymbol{H}_r$ of the individual reactions in the adiabatic mode. Assigning values of $\Delta \boldsymbol{H}_r$ to the individual reactions taking place requires data at various extents of conversion and product distribution.

> Adiabatic flow reactors—tubular in configuration along the lines of the top diagram in Figure 21—are uncommon in fine chemicals/pharma processing, but lab-scale versions are useful to obtain lumped heat effects of systems of very fast reactions, and if truly approaching adiabatic behavior, the temperature profiles versus residence time can be the basis of scale-up. Another variation of the adiabatic flow reactor is shown in the ***second*** diagram, with the feed stream into an annular cross section for preheating by the exotherm taking place in the inner tubular section (e.g., industrial-scale oxidation of 2-methyl-5-ethylpyridine with nitric acid to yield nicotinic acid).

Flow reactors for fast and highly exothermic reactions often consist of three sections in series (often, as depicted in the ***bottom*** diagram of Figure 21): (a) a

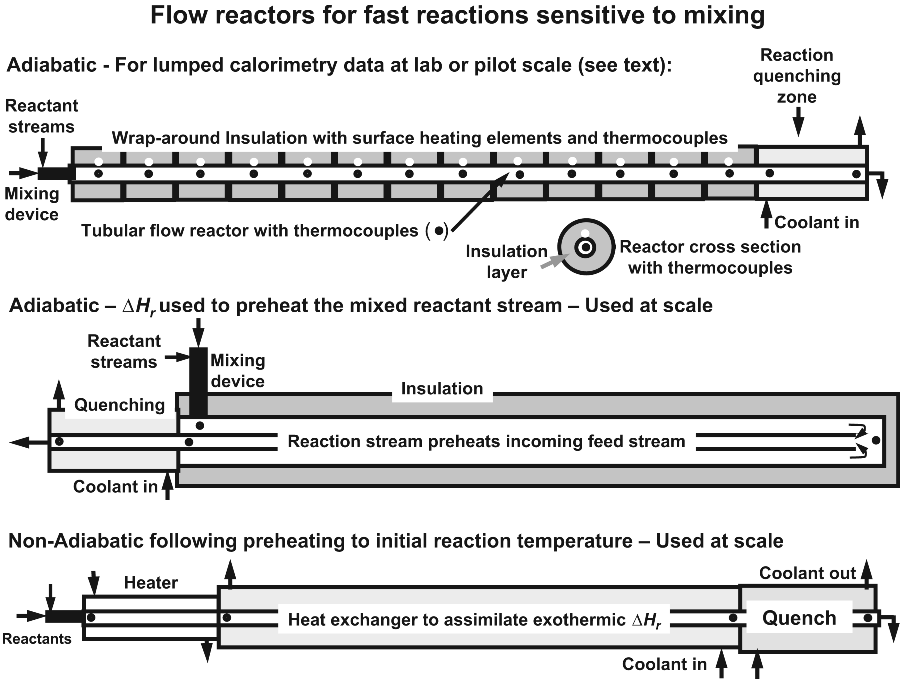

Flow reactors for fast reactions sensitive to mixing
Adiabatic - For lumped calorimetry data at lab or pilot scale (see text):
Reaction quenching zone
Reactant streams
Wrap-around Insulation with surface heating elements and thermocouples
Mixing device
Tubular flow reactor with thermocouples (●)
Coolant in
Insulation layer
Reactor cross section with thermocouples
Adiabatic – ΔH_r used to preheat the mixed reactant stream – Used at scale
Reactant streams
Mixing device
Insulation
Quenching
Reaction stream preheats incoming feed stream
Coolant in
Non-Adiabatic following preheating to initial reaction temperature – Used at scale
Heater
Coolant out
Reactants
Heat exchanger to assimilate exothermic ΔH_r
Quench
Coolant in

FIGURE 21 Tubular reactors, including a lab-scale adiabatic reactor for measuring the heat effects of fast exothermic reactions. In many cases back pressure is used to maintain the stream as a liquid phase (assuming minimal release of insoluble gases).

preheat exchanger for initiation of the reaction, (b) a cooling heat exchanger to assimilate the heat of reaction, and (c) a final cooler to either quench the reaction at some target product yield or cool it to a suitable work-up temperature.

Clearly, only the first of the three tubular reactor configurations can be used for calorimetry, but all three are suitable for scaled-up processing of highly exothermic reactions. There will be further discussion of flow reactors as sound choices for carrying out highly exothermic reactions that are unsuitable for batch or semibatch processing.

Finally, up-to-date pilot plants are often provided with enough digital control so that, in the manner of the process calorimeter, energy balances can be ***calculated***, but under no circumstances should we be tempted to ***first*** learn what the energy balance might be at that scale of operation. Indeed, scaling up of thermochemical hazardous processing must not take place unless we have at least "ballpark" figures as to the onset, magnitude, and rate of the energy releases—intended and unintended—and the risk associated with that scale of operation fully considered and taken into account. Indeed, a sound rule of thumb is not to go into the kilo lab scale without a ***first-level thermochemical hazard assessment***, which we will define soon hereafter.

By now we have set down the necessary foundation to address the specifics of thermochemical hazards assessment, their avoidance, or, as is often the case, the means of dealing with them in chemical processes that operate safely, namely, at a defined and acceptable level of risk.**

V. THERMOCHEMICAL HAZARDS AND THEIR ASSESSMENT

At this point there is no need to restate the formal definition of thermochemical events (i.e., the heat effects associated with chemical reactions at large). Indeed, our awareness of the world around us teaches that that chemical compounds—whether those in the business end of a match, a jerrican of gasoline, or a stick of dynamite—can be reservoirs of energy that can be released in amounts and at rates that seem to transcend the mass involved; the thermochemical energy instead relates to the particular compounds and their reactions, the undoing and making of chemical bonds (do recall the simple depictions in Fig. 5). We are also well aware, long before being exposed to the material in this chapter, of fires from spilled fuels, fires and explosions in petroleum refineries, household explosions from natural gas leaks, explosions in coal mines and grain silos, and the destructive power of artillery shells that pack relatively small masses of some chemical reactants way up on the energy scale in Figure 5.

Alas, there is less awareness of the thermochemical hazards in chemical processing. For instance, consider the following report (17):

> "Chemical Plant Blast Kills 22 People
>
> A 28 July 2006 explosion at a chemical plant in Jiangsu, China, killed 22 people and injured 29 others. The facility was in the process of starting up production of fluorobenzene, an explosive material used in pharmaceutical and agrochemical production..."

Although the brief news report goes on to focus on fluorobenzene as an explosive compound (actually, not unlike most low molecular weight aromatics when mixed with air in the right proportions), subsequent reports suggested that the fatal explosion was related to the start-up of ***chemical reaction processing*** early in the synthesis of the various halogenated (chloro- and fluoro-) benzenes in the plant's product line. Although out of the ordinary in the number of fatalities at the plant site, such thermochemical accidents are not that infrequent, as perusal of the Web site of the U.S. Chemical Safety and Hazard Investigation Board (18) reveals.

But let us come to the point: ***chemical processing of organic compounds presents hazards arising from the releases of energy by a range of chemical reactions. Of these, some are part of the intended process, but others are not and take place only by mishap***. The assessment of both kinds of hazards will be the main focus of the rest of this chapter, although we will also briefly discuss the rest of Table 5, as well as address the ABCs of risk reduction for all thermochemical hazards, albeit only briefly for those that have well-established prevention methods (e.g., fire and explosion) or that are encountered less frequently in our context (e.g., dust explosions). It is the last category in Table 5—the sort of events at Seveso and Bhopal—that will preoccupy us most.

A. Fire and Explosion Hazards

As per Table 5, we usually associate fire and explosions as the result of ***mixtures of air and a fuel***—that is, a chemical compound (or compounds) that can enter into combustion reactions with the oxygen in the fuel/air mixtures and release large heats of combustion with the generation of many moles of, ***mostly***, water, CO_2, and lesser amounts of other gases, depending on the molecular makeup of the fuel (recall the generalized reaction equation for combustion in Fig. 11). If

TABLE 5 The Thermochemical Hazards in Bulk Drug Processing

Fire and explosion arising from flammable mixtures of a range of organic compounds with oxygen, almost always from mixtures of compound vapor/gas with air. The reactions at hand are fast, highly exothermic combustions to gaseous products—thus the potential to go from fire to explosion. Awareness of these hazards and risks is generally high in the likely operating environments, which are generally tightly managed and regulated. Hydrogen, although a versatile organic synthesis reactant, presents extreme fire and explosion hazards.

Exothermic decomposition of unstable compounds over a wide range of kinetics and magnitude of the energy release—from slow self-heating reactions to detonations upon slight provocations. The range of structures, their mixtures, and particular conditions is quite wide, although knowledgeable scrutiny of the structures at hand and the literature can raise cautionary flags to sharpen the hazards the hazards assessment.

Dust explosions of stable compounds, their causes directly associated with the atypical high surface area of the compounds or materials (e.g., Mg, Fe, and other metals, coal, grain chaff, sugar), and their reactive mixtures with air. These explosions are most unusual in our context and can be readily prevented by awareness, tight containment of the powdery materials, and good housekeeping.

Fast exothermic reactions from inexpert handling of highly reactive chemicals—alkali metals, special reduction reagents, cyanogen chloride, chlorosulfonyl isocyanate, diketene, azides, and a myriad of other specialty reagents of organic synthesis, including the less exotic but hazardous category of water-reactive agents (thionyl chloride, sulfur trioxide, etc.). Fortunately, awareness is usually high when handling such reactants, and the necessary precautions are the rule.

Intended process runaway reactions and unintended reactions outside the conventional safe process envelope. Here the range of thermochemical hazards is as wide and rich as organic synthesis proper. Awareness has to be gained through comprehensive hazards assessment, and often a hazardous process must be chosen. Skillful scale-up, process design, and operation are a must.

oxygen availability to the fire is limited, less complete combustion tales place and some CO and carbon soot result—here you may recall the simple experiment conducted with the setting of a Bunsen burner: abundant air gave a blue flame (complete combustion), and limited air gave a yellow and orange flame from which carbon soot could be captured on a watch glass (incomplete combustion).

The combustion of many organic compounds is highly exothermic and generates a large volume of gaseous products. For instance, 1 g-mol of benzene generates, upon complete combustion, 6 moles of CO_2 and 3 moles of water vapor, as well as ~780 kcal/g-mol. But whether an ignited pool of liquid benzene burns slowly or rapidly or results in an explosion depends on the amount of benzene, the availability of oxygen, the rate of dissipation of the heat, and the rate of pressure increase from the water and CO_2 gas phase generated.

> At this point it seems best to ***carefully*** review Table 6—a fire and explosion miniglossary. We will continue without further elaboration of those terms, using them as if well understood.

Flammable organics are a factor in cases of fire and explosion in our context of chemical processing, although lesser than they are in petroleum refining, where most process streams are flammable and handled at far greater throughputs, often well above their flash point and some times above their autoignition temperatures, which means a leak is a probable fire. Indeed, fires and explosion in petroleum refining plants are not rare.

TABLE 6 Fire and Explosion. Frequently Used Terms and Their Definitions

Autoignition temperature—the temperature at which a given flammable mixture will start combustion without an ignition source, as it has a sufficient heat content to self-ignite.

Ignition—the event by which a flammable mixture comes into contact with a source of sufficient energy (e.g., a hot object, a spark, a lit cigarette, an ember from a distant fire) and combustion is initiated.

Explosion—very rapid generation and expansion of gas that generates a pressure shock wave.

- ***Chemical explosion***—an explosion that originates from a very fast chemical reaction with gaseous products at the reaction and subsequent conditions.
- ***Deflagration***—an explosion resulting in a shock wave that moves at a speed ***lesser*** than the speed of sound.
- ***Detonation***—an explosion resulting in a shock wave that moves above the speed of sound.

Mechanical explosion—an explosion due to sudden failure of a vessel upon a sufficient internal pressure. The events that follow depend on the nature of the mixture released from the vessel and range from just a release of gas or gas and liquid to fire or explosion of the released material.

Flash point (of a liquid)—the lowest temperature at which a liquid gives off enough vapor to create a flammable mixture with air that, upon an ignition source being present, will ***initiate (i.e., ignite)*** combustion of the mixture.

Flammability (flammable)—the composition of a fuel/oxidizer mixture (usually a fuel/air mixture) that can be ignited ***and*** the resulting point combustion can propagate through the rest of the unreacted mixture. An ***almost flammable*** mix may ignite, but the point combustion will ***not*** generate enough heat to self-sustain and propagate. See Fig. 22 for a definition and discussion of the ***lower*** and ***upper flammability limits*** of a fuel/oxidizer mix.

Safe process envelope—a boundary around the conditions chosen to ensure processing without untoward events such as runaway reactions, accumulation of unstable materials, etc.

In our context of bulk drug chemical processing, apart from incidents of inadvertent leakage, bad housekeeping, or bad maintenance—matters for which sound practices and rules exist—there are instances in which a ***chemical reaction mishap*** results in the release of flammables and ***subsequent*** fire or explosion—thus the care exercised in the selection of solvents for organic synthesis. For instance, let us consider Table 7, in which we compare the properties of acetone and diethyl ether, both suitable solvents for some organic reactions. Examination of Table 7 teaches us that diethyl ether if far more flammable than acetone (a much lower flash point), more easily evaporated if

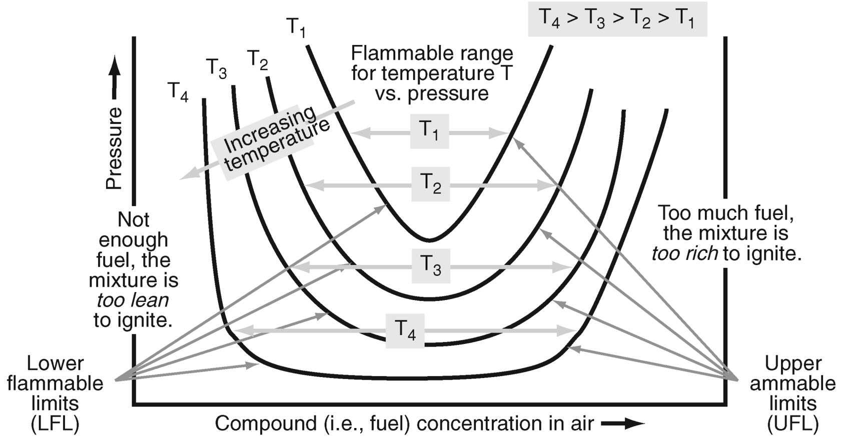
TABLE 7 Comparative Flammability Properties That Determine the Risk of Fire and Explosion—Acetone Versus Diethyl Ether

Let us consider the different properties of acetone and diethyl ether and then rank the two compounds as to which presents the greater hazard of fire and explosion

	Acetone	Diethyl ether
Molecular weight	58.1	74.1
Liquid density at 25°C, g/mL	0.79	0.71
Vapor density (relative to air)	2.00	2.56
Boiling point (1 atm), °C	56	35
Heat of vaporization, cal/g	132	84
Flash point (closed cup), °F	–4	–49
Autoignition temperature, °F	869	320
Energy release (full combustion), kcal/g	6.8	8.1
Lower flammable limit, vol% in air	2.6	1.9
Upper flammable limit, vol% in air	12.8	36

Fire and explosion hazards
Flammable mixtures with air

Compounds forming flammable mixtures with air generally do so as shown below, with the flammable range defined by the composition of the compound/air mixture, pressure and temperature. The area ***within*** each U-shaped curve is the flammable range of the mixture, with the curves defining the lower and upper flammable limits (LFL and UFL, respectively)..


$T_4 > T_3 > T_2 > T_1$
T_1
T_2
T_3
T_4
Pressure
Increasing temperature
Flammable range for temperature T vs. pressure
T_1
T_2
T_3
T_4
Not enough fuel, the mixture is *too lean* to ignite.
Too much fuel, the mixture is *too rich* to ignite.
Lower flammable limits (LFL)
Upper ammable limits (UFL)
Compound (i.e., fuel) concentration in air

Since a source of ignition always has a finite probability, the flammable fuel/air mixture
is the hazard for fire and possibly explosion.

FIGURE 22 Flammability of volatile compounds in mixture with air—a major and frequent hazard of chemical processing.

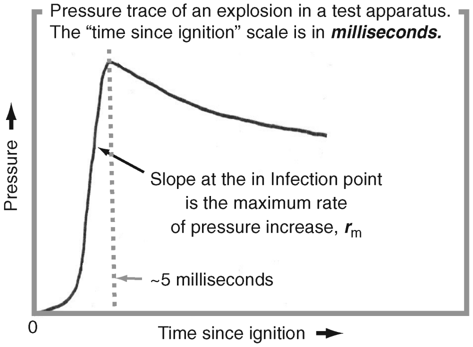
released (more volatile and with a lower latent heat of evaporation), with a wider ***flammable range*** in mixtures with air (Fig. 22), a much lower autoignition temperature, and a higher vapor density relative to air (more slowly dispersed from the point of release). Small wonder that diethyl ether is seldom used beyond the earliest synthesis work at the bench scale.

> There is an additional hazard with diethyl ether, arising from its capacity to spontaneously form small amounts of very unstable peroxides, which adds the risk of a chemical explosion to its use and to that of some other such solvents (e.g., tetrahydrofuran). We will soon discuss the category of chemical explosions, as per Tables 5 and 6.

Going for a closer look at Figure 22, ***we refrain from using*** the more common terms "explosive range," "lower explosive limit (LEL)," and upper explosive limit (UEL)," for we do not wish to equate flammability of a mixture with it being explosive—ignition does not imply explosion in every case, since having or not having an explosion depends on the circumstances at hand. If the flammable mixture ignites within an enclosure (e.g., a process vessel, an enclosed processing area in a building), the result may be explosive, with generation of a shock wave. It would be rare (and quite risky) for organic reactions in flammable media to be carried out in a process vessel with sufficient oxygen to permit ignition and propagation into an explosion within the vessel, with the

Characteristics of an explosion

As many as ten distinct parameters can influence the explosive characteristics upon ignition of an air/fuel mix with an enclosure – a process vessel or a building. Testing in a pressure vessel with fast response p and T sensors at the inner wall is done to obtain useful data on the explosive character of the test mixture (e.g., a metered mix of air and volatile components that is brought to the desired temperature before ignition).



a.- Mix composition is varied to obtain the lower and upper limits of flammability (Fig. 22).

b.- The minimum oxygen concentration for ignition may be also determined to obtain the requirements for rendering the mix inert with nitrogen or other inert gas.

c.- The maximum rate of pressure rise r_m allows comparison of the behavior of different mixtures and permits design of relief venting systems and of suppression provisions (injection of quenching gas).

d.- Application of the constant ***K*** for scale-up as shown below:

Such data most frequently follow the so-called "Cubic Law":

$(r_m)V^{1/3}$ = **constant** = ***K*** **The deflagration index** K_g for a vapor or gas **(10.14)**

K_{st} for a solid (that creates a dust)

Thus, for an explosion of the ***same*** air/fuel mix in an enclosure:

$[(r_m)V^{1/3}]$ in the enclosed space = $[(r_m)V^{1/3}]$ from the test **(10.15)**

which permits the design of ***explosion venting systems*** for scaled-up enclosures (vessels or buildings).

FIGURE 23 Measurement of the explosive potential of compounds, including those capable of dust explosions.

risk of overpressure and, at a minimum, risk of failure of the vessel closure. In such case, flammables may be released into the processing area, a fuel/air mixture realized and ignition always a possibility, leading to derivative risks of fire and explosion outside of the process vessel—thus our interest in learning about the likelihood of explosion and its scope, which we can estimate from testing as per Figure 23 (2,16). At any rate, if working with an ***unfamiliar*** but potentially flammable mass, assessment of its flammability and, if flammable, of the immediate consequences of ignition is necessary. Nonvolatile or low-volatility process masses reasonably dilute in well-characterized flammable solvents may not require such testing, but their expected and probable compositions should be scrutinized for potentially troublesome components and their flash points determined.

Finally, on the hazards of fire and explosion from flammable liquids, vapor, or gas streams, we should note that mists or sprays of very small droplets in air—which sometimes develop in chemical processing—usually exhibit greater flammability (i.e., lower flash points) than the bulk liquid from which they originate, and, as a sound guideline, the generation of such process streams should be avoided (20).

Obviously, the processing of flammable streams (or process masses) is widespread in chemical processing, including that of our pharma context. Indeed, rigorous methods of assessing such hazards and their risks have been developed (20), albeit unavoidably relying on reasonable approximations often enough. For example, flammable liquids are pigeonholed into four categories of flammability hazard according to ranges of flash point and volatility (i.e., atmospheric boiling points), and a great deal of what follows is based on lumped numerical factors from each pigeonhole of flammability that, in turn, are used in conjunction with other lumped quantities reflecting factors other flammability (e.g., reactivity or instability of the compounds in the process) (20).

B. Dust Explosions

Just as stated for an air mass or stream laden with a mist of liquid droplets or spray, an air mass laden with finely divided solids may present a clear explosion hazard, as evident by well-known incidents in coal mines and grain silos, where mixtures of air with fine dusts of coal and grain chaff, respectively, explode on occasion. Indeed, dust explosions may also take place wherever finely divided organic solids and air can mix so as to disperse the fine solid particles, as shown by recent fatal explosions of polyethylene powder dust and sugar dust that became suspended in air, ignited, exploded, and so rattled the buildings that other dust, settled and accumulated over time throughout the facilities, became suspended and ignited, with destructive secondary explosions and fires taking place, resulting in 18 fatalities and a large umber of injured and ruined facilities. The most notorious case, a long time ago, was a Wrigley's chewing gum plant in Brooklyn, New York, that had so much gum dust settled over practically every surface (rafters, pipes, shelves, etc.) that a small local explosion resulted in secondary explosions that propagated rapidly through the rest of the multistory building. In other words, ***good housekeeping matters*!**

Thus, testing of the explosive characteristics of ***fine powders*** that might be mixed and ***dispersed*** in air in our chemical processing is advisable. Indeed, as indicated in Figure 23, the testing procedure for such mixtures mimics that used for the study of air/vapor mixtures (the apparatus is, of course, not identical). The same kind of data are obtained, the corresponding deflagration index K_{st} obtained, and the same follow-up carried out in scale-up and design of venting and other mitigation measures in case of explosion, all of which is summarized in Figures 23 and 24. As one would expect, the likelihood of flammability is a sensitive function of the particle size distribution (PSD) of the solids—the finer the PSD, the easier it is for the solids to disperse less unevenly through the air volume and to have a larger surface area for ignition and the combustion reactivity to follow. Indeed, the said methods of risk assessment (20) actually assign lumped ***dust explosion penalty*** factors that enter into the overall risk assessment calculations—thus the eightfold ***increase*** in the penalty factor as the particle size of the solids at hand ***decreases*** from >175 μm to <75 μm. Finally, Table 8 provides a summary of the key issues in dust/air flammability and explosion potential.

Although it is in the bulk drug finishing steps that drying, milling, blending, and vacuum conveying of solids are carried out, those operating areas are normally designed with a minimum of surfaces for dust accumulation and also operate with rigorous housekeeping on current good manufacturing practices (cGMP) grounds. Other parts of the plant, however, are not to the same norm and require more vigilance with respect to accumulation of organic powders, even if current regulations as to personnel exposure have greatly improved solids handling and containment.

Explosions (dust and otherwise) in vessels or enclosures

Prevention: - Operate with the solid/air mixture outside of the flammable range.
- Reduce $[O_2]$ to safe level by inert gas or suppressant addition

Suppression: - Introduce suppressant gas or other material (e.g., $NaHCO_3$ powder) upon detection of pressure surge or flame. Extremely fast response sensing and action are needed (see the time scale in Fig. 23).

Mitigation: - Explosion venting (rupture disc, blow-out panels or lids, etc.). Consideration must be given to where direct the vented materials. Vent area and rating are critical.
- Isolation of the explosion so it cannot propagate throughout the facility. This is done in conjunction with venting.
- For relatively small vessels, it is feasible to build them with sufficient strength and closure integrity to withstand the explosion pressure $\mathbf{\Delta P_{ex}}$ without rupture or significant deformation

A Vent area is large enough and the pressure is relieved OK.

B Vent area is too small and the pressure exceeds the rating. Vessel may deform, enclosure damage possible.

C Vent blocked. Pressure equals or exceeds the safety margin above the rating. Total and sudden vessel or enclosure failure.

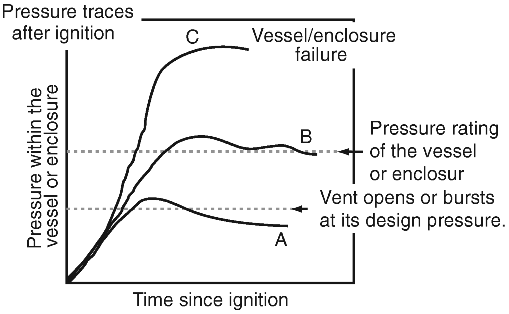


FIGURE 24 The risk of explosion within vessels or enclosures. Providing sufficient venting capacity (rupture discs and relief valves for vessels, blowout panels for enclosures) requires the kind of data discussed in Figure 23.

TABLE 8 Key Factors in Dust Explosions—Flammable Mixtures From Dispersed Solids in Air

Chemical processing includes *solids processing* (filtration, drying, particle size reduction and classification, conveying, blending, hopper storage, packaging, charging from bulk containers, subdivision, particle size enlargement, etc.).

Many of these operations include the creation and handling of mixtures of dispersed solids and air (some milling, drying, and conveying operations) or their unintended formation by dusting, inadequate containment, or accidental releases of dispersible solids.

Organic solids of fine particle size and dispersed in air may form flammable mixtures that can explode if:

- The particle size distribution of the solids *is fine enough* to permit flame propagation.
- The solids are *sufficiently dispersed* throughout the volume of the mixture. Unlike a vapor/air mix, solids may disperse unevenly in air mixtures and, in the extreme, settle down.
- A *sufficient* source of ignition is present.
- As vapor/air mixtures (Fig. 22), an explosive solids/air mixture *must be within a range*—not too lean in solids fuel or too lean in oxygen (too many dispersed solids).

Although seemingly constrained by the above requisites, the *hazard* of solids/air explosion (i.e., *dust explosions*) exists in our processing context, but explosions are rare

C. Hazards from Highly Reactive or Unstable Compounds

The scope of organic synthesis in pharma includes such a wide range of compounds and materials that inevitably one deals with many highly reactive or unstable compounds—reactants, catalysts, intermediate products, and some auxiliary chemicals. The opportunities for chemical mishap are abundant in such an environment, and processing practices must be based, first and foremost, on keen ***awareness*** of any hazardous properties of all materials handled. We will address the energetics of carrying out chemical reactions in short order, but at this point we will discuss the ***hazardous chemicals and materials at large***. Let us look first at chemicals and materials with ***minimal*** attention of their chemical structures, for that discussion will follow and will be approached differently.

1. Vapors and Gases

Flammability, which we discussed earlier and depicted in Figure 22, is the key hazard when processing gases and vapors in the presence of oxygen (usually by mixtures with air). Apart from what we discussed on and about Figure 22, we should recall that a flammable mixture arises only when the combustion at the point of ignition can propagate. Heat dissipation to an unreacted mixture surrounding the point of ignition, if greater than the heat of combustion, inhibits propagation, and the mixture is not flammable, which explains the general shape of the curves in Figure 22: (a) increasing temperature accelerates the rate of combustion and thus facilitates propagation into the unreacted mixture and enhances flammability and (b) pressure has a much milder enhancing effect, but a ***minimum oxygen concentration*** is needed to support propagation (as shown by the absence of flammability at low total pressure, at the bottom of Figure 22). This latter fact is the basis for the practice of blanketing flammable liquids with inert gas, thus reducing the oxygen concentration in the overhead vapor phase below the threshold for propagation of ignition. Hydrogen is an extreme case of gas flammability, which explains the practice of reducing oxygen concentration in the overhead space if hydrogenation reactors by repeated vacuum and inert gas purge cycles before admitting the hydrogen reactant.

2. Liquids

Apart from the ability of many liquids to generate flammable vapor phases, as measured by their flash point (Table 6), there is the related hazard of autoignition (Table 6). We should be aware of the autoignition temperature of our process streams, for fire and explosion can occur upon inadvertent heating liquid process masses to their autoignition temperature [(4), p. 187].

Impact and shock can also cause unusually sensitive liquids to ignite well below their autoignition temperature, and impact stress testing is used to determine the sensitivity of suspect liquids (because of their structure or anecdotal information). Examples of such liquids are nitromethane (modestly sensitive) and nitroglycerine (extremely sensitive) [(16), p. 42]. The simplest way to handle such liquids is by significant dilution if the process allows it. Shock sensitivity is also exhibited by certain liquids, and suitable tests methods exist [(16), p. 93].

Compression of some liquids (the usual suspect structures again; e.g., nitromethane) can cause detonation of the compressed vapor phase above the liquid, and pumping or subjecting such liquids to the water-hammer effect is quite hazardous [(16), pp. 42–43].

3. Solids

Apart from rapid exothermic decomposition (up to explosion) when heated, many solids also exhibit sensitivity to impact, shock, and friction—actions that can impart sufficient energy to set off the fast decomposition reaction that propagates throughout the total mass of the material. Explosives are, of course, the best examples of such materials, but some compounds used or that arise in organic synthesis (e.g., azides) exhibit these sensitivities, which can be assessed by various methods [(16), pp. 92–94]. Another category of hazardous solids are pyrophoric catalysts—solids having such active sites on their surfaces that rapid adsorption of oxygen and ignition take place with ease, and special procedures for their handling and charging to process vessels with flammable liquids are necessary. Many such catalysts (e.g., Pt or Pd on activated carbon, Raney copper or Raney nickel) are stored wet or under water. On the other hand, water-reactive solids (e.g., metallic sodium) are often handled dispersed in mineral oil.

D. Assessment of High-Energy Compounds from Their Structures

Many organic compounds can decompose with ease and with a large energy release, up to detonation. Collectively known as ***high-energy*** compounds, we are wise to know if they are among our reactants and products, or perhaps likely to form as by-products in our reactions. Various methods exist to predict or rank the potential instability of compounds, such as the ***oxygen balance*** (O_2 balance). This method consists of calculating from the molecular formula if the compound itself contains enough oxygen to convert to its simplest decomposition products, generally those of complete combustion, and without the participation of oxygen from other sources (e.g., air, oxidizing agents). If the molecular formula contains all the needed oxygen (**O_2 balance = 0**) or more (**O_2 balance > 0**), the compound is deemed to be of ***high energy*** and probably prone to exothermic decomposition, often with little provocation. It certainly is a simple exercise to carry out, although by no means all that reliable, nor does it account for so many structures that are quite short of oxygen (**O_2 balance < 0**) but are also quite capable of highly energetic decomposition and often with just as little provocation.

An alternative to such estimation methods is the use of the accumulated empirical knowledge of those ***structural features*** that, over time and much observation, have been tightly associated with the high-energy behavior. We can see such a compilation [(14), chap. 2, Table 2.5, p. 32], which, while not claiming to be exhaustive, is certainly comprehensive. Some of the structural features in the ***proven*** high-energy compounds category are listed below:

a. Poly nitro alkyl and aromatic compounds–$R(NO_2)_x$ and $Ar(NO_2)_x$, where $x > 1$
b. Other features rich in ***both*** N and O, such as –N–NO_2, –N–N=O, –C–O–N=O, –C–O–NO_2
c. Features rich in nitrogen: azides, tetrazoles, triazines, azo, and diazo compounds
d. Acetylenic bonds and halo-acetylenic bonds
e. Peroxides –C–O–O–C–, peroxyacids –C–O–O–H, and peroxyacid salts –C–O–O^-M^+
f. 1,2-Epoxides (far more sterically strained that 1,3–epoxides)
g. Difluoroamines –$N(F)_2$
h. Several other structural features, mostly rather uncommon

Scanning all the structural features in the said table [(14), p. 32] reveals quite a few that are rich in N or rich in O or rich in ***both***, but one is also struck by the wide variety of features that contribute to the serious hazard in the use or formation (whether intended or not) of high-energy compounds—thus the opportunity for collaboration between the experienced process chemist and the thermochemical safety specialist (preferably a chemical engineer) in ferreting out these hazards and, if present and unavoidable, assessing them fully and contributing to process scale-up and safe implementation.

E. Chemical Incompatibilities

Most chemical incompatibilities have to do with the potential of exothermic reactions, often vigorous (e.g., nitric acid and acetone, chloroform and strong alkali bases). A thorough check of a comprehensive listing (21) is an early item in our hazards assessment to-do list. Many of these incompatible situations depend on the specific conditions, and getting away with it at first does not mean all that much as process development goes forward. For example, chloroform and aqueous OH^- seem innocuous enough as immiscible phases, but it does not take much of, say, methanol to allow enough miscibility for a fast and substantial exotherm to take place. Oxidizing agents (e.g., H_2O_2, perchlorates, periodates, hypochlorites) are also hazardous. A good compilation of hazardous chemicals should always be handy (22).

F. Hazard Assessment Methods, Implementation, and Upkeep

Schemes for the assessment of thermochemical hazards are legion and varied, ranging from the basic to the rigorous and comprehensive. The process developers are confronted with the question of how much such effort should apply to a changing process—how much effort and how soon. Some early findings that call for follow-up effort may be tossed aside as soon as the process evolves. Yet, one needs to know just enough to ensure safe kilo lab operations, where hands-on work and expediencies (e.g., evaporate to dryness) mean greater personnel exposure and some thermochemical risks not taken in a more mature and engineered operation. To put this thorny issue in perspective, let us consider Figure 25, in which we depict the approximate accumulation of process know-how as a function of the process development cycle for a new bulk drug and place some basic milestones of thermochemical process assessment along the curve.

> Rather than repeat herein the basis for the ***process know-how curve***, the reader is referred to Figure 6 in chapter 2. We will, however, note that the ***100% know-how*** on the vertical axis refers to the know-how required for New Drug Application (NDA) approval and for safe, timely, and effective ***first*** manufacture—let us call it ***the first-generation process***. Obviously, a longer development cycle and manufacturing experience at scale will accumulate more process know-how, often leading to a second-generation process as the product grows and greater bulk drug output is sought. Conversely, that better process set aside during development by the time-to-market imperative could also come forward after further development as the sufficiently different and superior ***second-generation process***, bringing its own hazards assessment and tech transfer package.

A different perspective of the task of thermochemical hazards assessment is offered in Figure 26, this time defining to some extent the specific assessment tools as they are applied through the process development cycle. For our purposes, Figures 25 and 26 define well enough the sequence of events in ***thermal hazards assessment*** of a process under development. More detailed schemes are

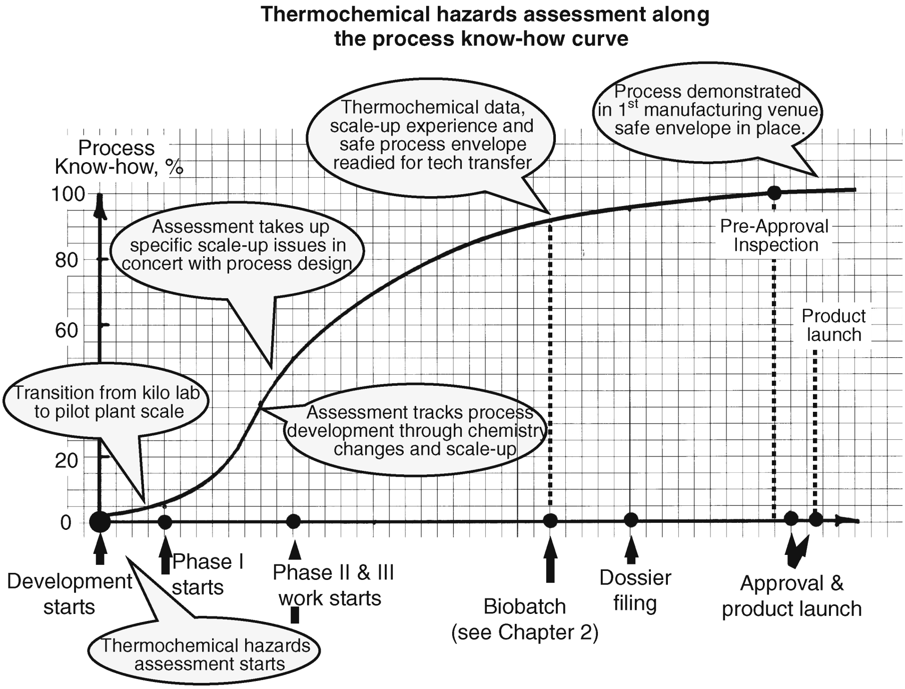


FIGURE 25 The accumulation of hazards and risks know-how along the process development cycle for a bulk drug. Note the need for development and process design to collaborate to properly assess the risks of hazards that seem acceptable before process design.

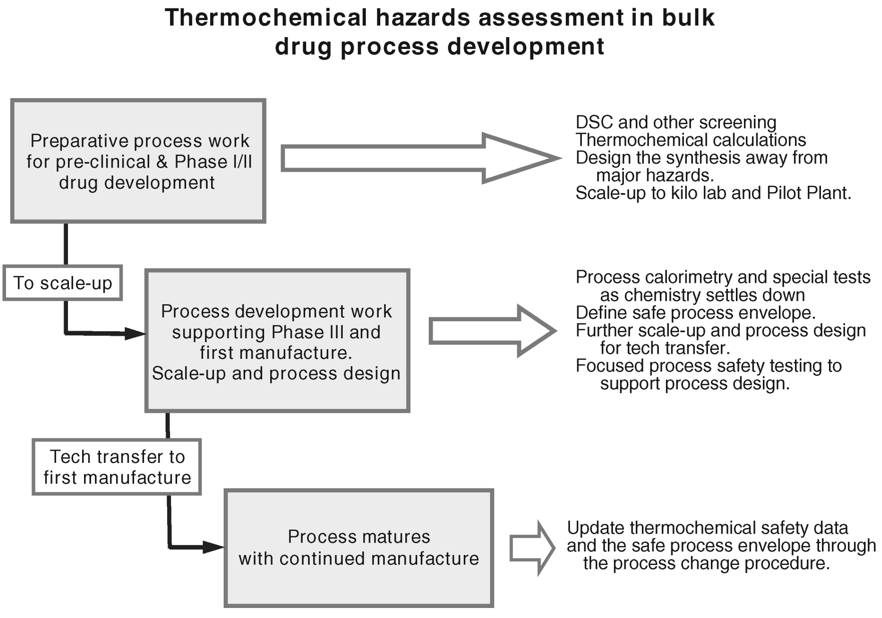

Thermochemical hazards assessment in bulk drug process development
Preparative process work for pre-clinical & Phase I/II drug development
DSC and other screening
Thermochemical calculations
Design the synthesis away from major hazards.
Scale-up to kilo lab and Pilot Plant.
To scale-up
Process development work supporting Phase III and first manufacture. Scale-up and process design
Process calorimetry and special tests as chemistry settles down
Define safe process envelope.
Further scale-up and process design for tech transfer.
Focused process safety testing to support process design.
Tech transfer to first manufacture
Process matures with continued manufacture
Update thermochemical safety data and the safe process envelope through the process change procedure.

FIGURE 26 Hazards assessment along process development—another perspective.

proposed in the literature, of which we select one for further consideration by the reader [(4), p. 21]. A scheme focused on the ***risk assessment*** of identified thermochemical hazards is also offered to the reader [(1), p. 73].

> In the latter reference, Stoessel uses a ***criticality factor***, one of those lumped attributes that assign, in his case, the severity of the risks associated with a thermochemical hazard, and as we stated more than once, in his criticality factor scale of 1 to 5, a factor of 5 calls for abandoning the particular process operation at issue, whereas factors of 3 and 4 accept the hazard and the process goes forward into scale-up and process design for ***safe*** implementation at an acceptable level of risk.

Generally, however, all schemes for hazards assessment move along the broad outlines of Figures 25 and 26, that is, the more specific tools beyond screening are applied as the process is better defined and individual process safety issues come into sharper focus. Finally, perhaps the most difficult aspect of hazard assessment is its ***upkeep*** as the process evolves, for keeping the hazards assessment ***fully up to date*** is a significant task that requires discipline, particularly as there is a lot of devil in the details, as the example that follows illustrates. Beyond the imperative of conducting safe pilot plant work (sometimes up to the 10,000 L batch scale), there is the imperative of transferring into process design and tech transfer to first manufacture a ***complete*** thermochemical hazards body of knowledge. Vigilance and good judgment needs to be exercised by the overall process team in following every zig and zag of the development cycle, selecting judiciously what deserves testing anew and getting any significant alteration of the safety profile of the process promptly incorporated into the process design already underway (Fig. 25).

> What follows is an actual example of the devil in the details of thermochemical hazards assessment and of the need to remain vigilant as to the zigs and zags of the chemical process through the changes during development and through its life well past tech transfer into first manufacture.
>
> An azo compound, with the structural feature –C–N=N–C– and particularly rich in neighboring nitrogens (an obvious ***usual high-energy suspect***) was well into first manufacture, isolated by conventional methods from the aqueous diazotization reaction mass at a large semicommercial plant scale. At some point corrosion somewhere in the processing train caused the isolation procedure to be switched from aqueous HCl to aqueous H_2SO_4, a seemingly trivial change in the isolation, as the acid was totally washed off before the solid azo compound was isolated by filtration, washed with copious water, and taken to batch vacuum drying in about 1500 kg charges. The process change material from lab front runs was taken through the DSC screen and no change found in the onset of its large decomposition exotherm, about 50°C above the well-controlled maximum and terminal drying temperature. Alas, the first process change batch decomposed explosively as the drying cycle was being completed, with significant consequences. Thorough and prompt investigation revealed that the screening DSC test missed the much earlier decomposition onset of the process change material—the scanning rate was much too fast to detect the difference. Indeed, the rather messy crystalline structure of the isolated compound was messier enough upon the process change, making the high-energy solid more labile.
>
> We will revisit the issues of upkeep of the thermochemical process safety profile and the process change management at the end of the chapter. But the point has been made—***details matter***.

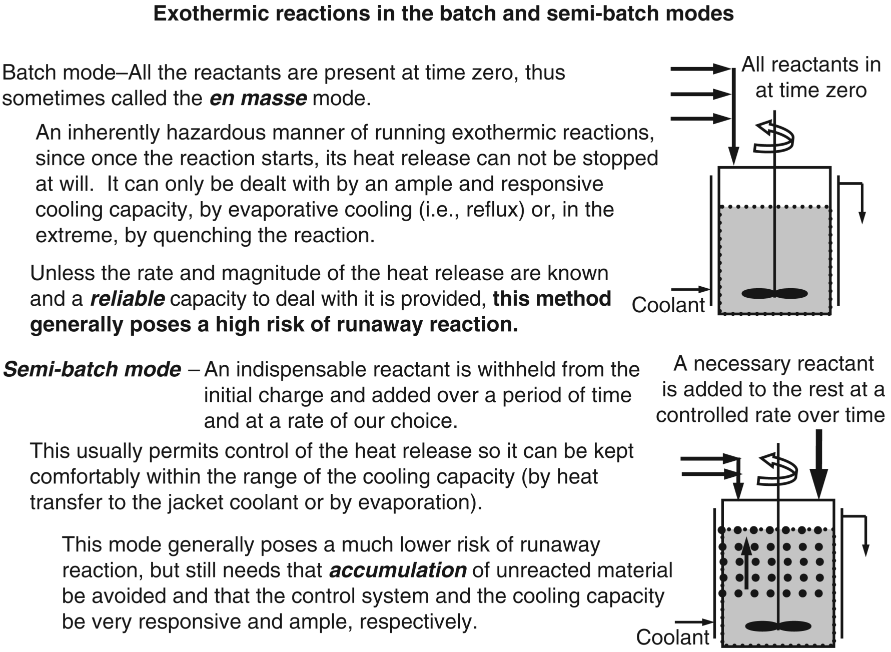
VI. EXOTHERMIC REACTIONS—RUNAWAYS AND UNINTENDED REACTIONS

From the variety of thermochemical hazards we have described or mentioned so far, ***runaway reactions*** stand out as the probable driving force for the coalescence of thermochemical process safety as a technology that happily marries chemistry and chemical engineering, a most fortunate development for pharma's chemical processing. Still, runaway events are not rare: recall the 2006 explosion previously mentioned (17) with 22 fatalities and a greater number of injured. Perusal of the Web site of the Chemical Safety and Hazard Investigation Board (18) reveals that reaction runaways happen often enough and just as often with consequences—thus our dedicating a fair share of this chapter to the subject.

Then there are those ***unintended reactions***, sometimes inevitably following a runaway event, but also arising from various other reasons that need to be at least highlighted herein. Altogether, these two kinds of events account for much grief and loss in our context of chemical processing.

A. The Batch Mode of Running Chemical Reactions

With few exceptions—when compelled by manufacturing volume, process necessity, or advantage—chemical reactions in pharma are run in one of two modes, as depicted and briefly described in Figure 27 in the context of running exothermic reactions. As the text in the figure makes clear, the risk of a runaway event in the ***batch mode*** (sometimes called the *en masse* mode) is seemingly obvious: ***all the potential heat of reaction is in place*** as soon as all the reactants



Exothermic reactions in the batch and semi-batch modes

Batch mode–All the reactants are present at time zero, thus sometimes called the ***en masse*** mode.

An inherently hazardous manner of running exothermic reactions, since once the reaction starts, its heat release can not be stopped at will. It can only be dealt with by an ample and responsive cooling capacity, by evaporative cooling (i.e., reflux) or, in the extreme, by quenching the reaction.

Unless the rate and magnitude of the heat release are known and a ***reliable*** capacity to deal with it is provided, **this method generally poses a high risk of runaway reaction.**

Semi-batch mode – An indispensable reactant is withheld from the initial charge and added over a period of time and at a rate of our choice.

This usually permits control of the heat release so it can be kept comfortably within the range of the cooling capacity (by heat transfer to the jacket coolant or by evaporation).

This mode generally poses a much lower risk of runaway reaction, but still needs that ***accumulation*** of unreacted material be avoided and that the control system and the cooling capacity be very responsive and ample, respectively.

All reactants in at time zero
Coolant
A necessary reactant is added to the rest at a controlled rate over time
Coolant

FIGURE 27 The principal chemical reaction modes in bulk drug processing.

are charged. Indeed, a simple calculation reveals the ***worst-case*** scenario as to the ***hazard of a runaway*** event and the ***severity of the risk***. To wit, let us go back to our first example in Figure 10 (hydrogenation of nitrobenzene to aniline) and quickly calculate the ***adiabatic temperature rise*** $\Delta \boldsymbol{T}_{\mathbf{ad}}$ of the reaction mass upon complete conversion of the reactants (i.e., there is no exchange or dissipation of the heat released during the course of the reaction). Thus equation (**10.8**) quickly tells us the maximum temperature rise of the reaction mass if all the heat of reaction goes into sensible heat (i.e., temperature increase). Using our example from Figure 10 and running the reaction neat (i.e., undiluted) as one would:

Reaction mass basis is 1.0 kg-mol of nitrobenzene + 2 kg-mole of H_2
Mass $M \sim$ (123 kg of nitrobenzene + 4 kg of H_2) $\sim$ 127 kg

Total heat released = Q_r = (133 kcal/g-mol of nitrobenzene)
× (1000 g-moles of nitrobenzene)

Q_r = 133,000 kcal

Heat capacity $C_p \sim$ the average of the C_p of nitrobenzene and aniline $\sim$0.45 kcal/kg°C (19)

Therefore, by equation (10.8):

$\Delta T_{\mathrm{ad}} \sim (133,000)(127 \times 0.45)^{-1} \sim 2327°\mathrm{C}$
Unit sanity check (kcal) $(\mathrm{kg})^{-1}(\mathrm{kcal})^{-1}$ (kg)(°C) = °C

Given the atmospheric boiling point of aniline ($\sim$185°C), the worst-case scenario is one of a very large increase in pressure and temperature with inevitable vessel failure, probably explosive. Indeed, the $\Delta \boldsymbol{T}_{\mathbf{ad}}$ is so large so as to defy any imaginable cooling scenario that might be able to deal with it. Extreme at if may seem, the above is a sound "first-of-all" exercise upon approaching how to run an exothermic reaction, for it would rule out the batch mode straightaway. Instead, we would approach the semibatch mode, in which we would control the H_2 pressure and the gas/liquid mass transfer to be well within our cooling capacity under a suitable process control scheme (e.g., H_2 fed under vessel pressure control with a high-temperature shut-off or temperature control at a safe predetermined H_2 pressure). Indeed, various semibatch control schemes are available, including interlocks in the event of loss of coolant or agitation.

Review of the Web site of the Chemical Safety and Hazard Investigation Board (18) shows that runaway reactions in the batch mode are not all that rare, although incompetence is clearly at the root of the two incidents mentioned below.

Morton International, New Jersey. A textbook example of a batch mode exothermic reaction that ran away and got hot enough to trigger a secondary (and ***unintended***) decomposition reaction, also exothermic, that resulted in even higher temperature, fast excess pressure, explosive vessel failure, and secondary flammables fire and explosion. There were deaths and injuries. The secondary decomposition reaction was known and documented, but ***awareness of it did not reach the operating practice***. Had proper hazard and risk assessment been done, the energy balance would have led to abandoning the batch mode or, at a minimum, to a great increase in the cooling capacity and an update of the existing process control system—a manual practice of "initiating" the reaction with steam, then switching to cooling water at the right time. Such a method was actually reckless, and a history of lower-temperature excursions from the desired reaction was ignored.

> Synthron, North Carolina. A textbook example of how ***not*** to scale-up production. A batch mode exothermic polymerization, run in flammable solvents at their reflux temperature, was doubled up in batch size in the same equipment and without the requisite energy balance calculations. The heat release and the resulting vapor load overwhelmed the evaporative cooling system (water-cooled condenser for solvent reflux) and the relief venting, with an overpressure that loosened up the vessel manhole and the vapor piping, releasing hot vapors into the building, with subsequent explosion of the resulting solvent/air mixture. There was a death, and several were injured.

What can we learn from these costly incidents? Not so much about flawed management and poor judgment, although we will visit the teachings on those aspects of the problems in the sections "Thermochemical Hazard Avoidance, Prevention, and Risk Reduction" and "In Closing" of this chapter. The lesson we want to take home from what we just read is why and when is it safe to run exothermic reactions in the batch mode. Given the availability of the semibatch mode—not very much more difficult to run—why would we ever want to fill a reactor with so much potential thermochemical energy and then go on and sort of "tickle the dragon's tail," as those people at Morton did over and over? Or should we just reserve the convenient batch mode for endothermic reactions free of decomposition events in the DSC screening of its samples, totally unlike the bottom right corner DSC trace in Figure 20 and more like the one on the upper left?

Instead, let us take a closer look a these incidents and make up our minds about the batch mode. Because there are too many organic synthesis reactions that demand that all reactants be together at the outset if we are to obtain the desired chemical result, and thus avoid a tenacious impurity that renders our bulk drug unsuitable by today's expectations as to chemical purity.

> We are past getting high yields and purities >98.5%, for we now need consistent impurity profiles, since new impurities raise regulatory eyebrows. Usually no single impurity may be greater than some very low percentage, and some particular ones must be even lower. The selectivity of our chemical reactions transcends yield, and we need to run reactions at their best, which sometimes the semibatch mode does not do well, always running at low concentration of one of the reactants.

We will start with Figure 28, where the reaction heat release rate Q_r and the heat transfer through the surface of the wetted and jacketed wall of the stirred tank Q_{ex} (do recall the energy balance in Fig. 15) are plotted as a function of the reaction mass temperature. If the reaction mass temperature is allowed to increase, the reaction rate constant will also increase and we can see the Arrhenius equation terms multiplying the reaction mass volume V, the heat of reaction ΔH_r, and the reactant concentration term C_r (a first-order reaction has been assumed for this discussion) so as to afford Q_r as equation (**10.16**). Then, of course, are the plots for the heat exchanged through the vessel wall, which is expressed by the familiar equation (**10.11**). As Q_{ex} will be approximately ***linear*** with the ΔT across the wall and thus approximately ***linear*** with the reaction mass temperature, there will be an inevitable crossover point with the ***exponential*** curve for Q_r. At that crossover the rate of heat released by the reaction mass ***exceeds*** the heat lost across the wall; that is, $Q_r > Q_{ex}$. This means that the temperature of the reaction mass will continue to ***increase indefinitely***—the reaction ***runs away***, and only two outcomes are

Runaway reaction from the intended chemistry
Exothermic reaction run in the batch mode

If the reaction temperature is not kept within the left side of the crossover point of Q_r and Q_{ex}, the opportunity is created for a runaway event, the consequencesof which can only be averted if the limiting reactant (i.e., C_r) is depleted soon enough or by immediate quench..

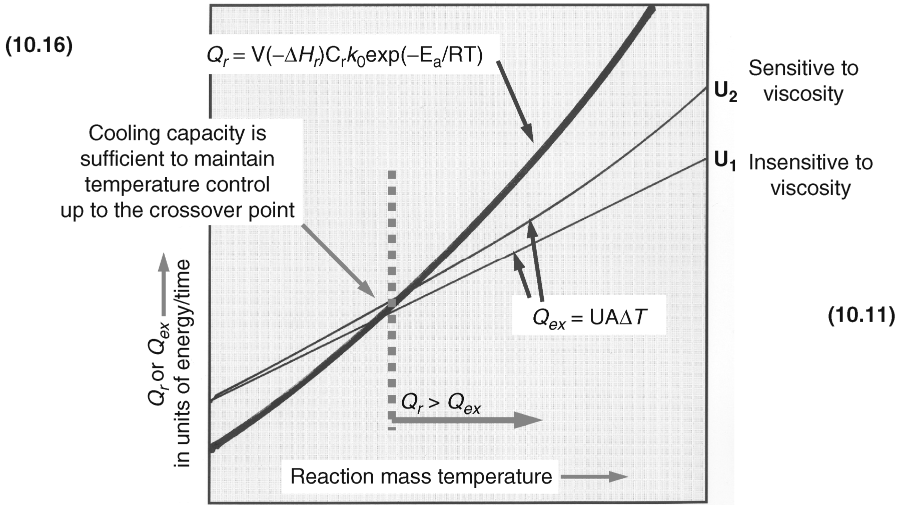


FIGURE 28 The runaway exothermic reaction in the batch mode.

probable—the reactants get depleted, or the reaction mass boils or gets hot enough to engage in organic decomposition reactions, usually with gas generation and overpressure in the vessel that may or may not be relieved on time, as per Figure 29. In the latter, case A depicts timely relief of the pressure (as in the Seveso incident), whereas case B depicts a very different scenario—insufficient pressure relief and failures of the closures in the system, the vessel itself, or both. Such were the outcomes at Morton International and at Synthron, the former taking place explosively (recall the miniglossary in Table 6), with secondary fire and explosion in both cases. Finally we come to Figure 30, depicting the Morton International event (and another failure scenario, the much dreaded and inopportune loss of cooling or, for that matter, loss of agitation, which is comparable to the loss of cooling but aggravated by the development of temperature differences within the reaction mass). At any rate, all the scenarios in Figures 29 and 30 describe ***loss of control*** over the temperature of the reaction mass and the energy balance.

Assuming we have compelling reasons to run the reaction with all the reactants together at the start—and there are such cases in organic synthesis—what options do we have to avoid the hazards, risks, and consequences we have just discussed? Well, such options exist as follows, ***all starting out with our getting a firm grasp (before the fact!) on the probable energy balance*** of the system being considered for scaled-up processing. If the probable energy balance indicates that we can operate at a safe distance from unintended

Runaway reaction with vessel failure

Consider a stirred tank reactor operating in the batch mode in which an exothermic reaction (with a significant ΔH_r) runs away –the rate of heat release catches up with the cooling rate as per the sequence of events in Fig. 28. The reactor set-up is shown at the left below, the same as that of the Morton International runaway case (no reflux condenser). Scenarios **A** and **B** are depicted.

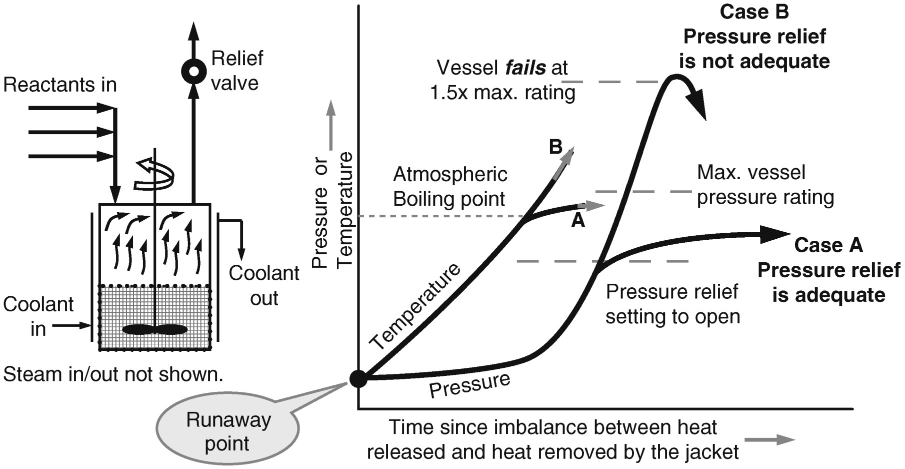

Reactants in
Relief valve
Coolant out
Coolant in
Steam in/out not shown.
Runaway point
Pressure or Temperature
Vessel *fails* at 1.5x max. rating
Case B Pressure relief is not adequate
B
Atmospheric Boiling point
A
Max. vessel pressure rating
Case A Pressure relief is adequate
Pressure relief setting to open
Temperature
Pressure
Time since imbalance between heat released and heat removed by the jacket

FIGURE 29 Vessel pressure outcomes from exothermic runaways. In most such events, upon opening of the relief devices both liquid and gas/vapor phases compete for the available cross-sectional area. The two-phase behavior of hazardous systems needs to be evaluated for proper sizing of venting devices.

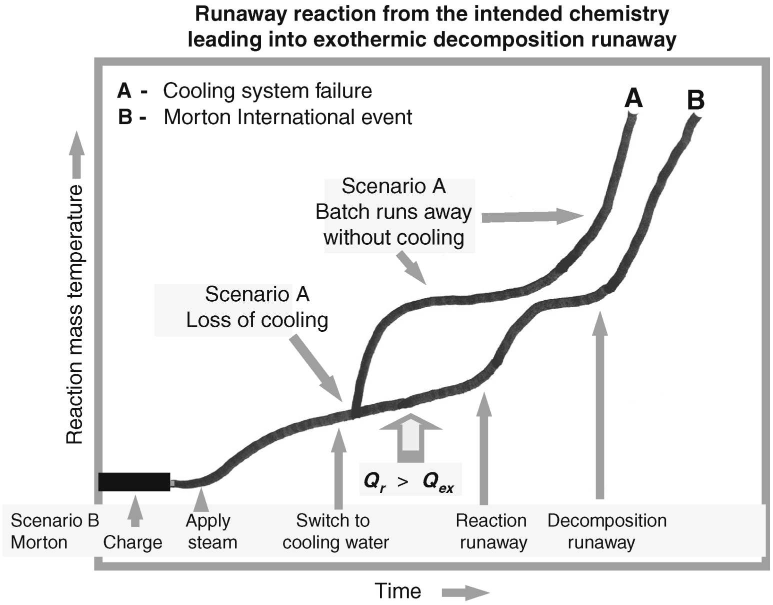

Runaway reaction from the intended chemistry leading into exothermic decomposition runaway
A - Cooling system failure
B - Morton International event
A
B
Scenario A Batch runs away without cooling
Scenario A Loss of cooling
Reaction mass temperature
$Q_r > Q_{ex}$
Scenario B Morton
Charge
Apply steam
Switch to cooling water
Reaction runaway
Decomposition runaway
Time

FIGURE 30 Exothermic batch runaway scenarios. The outcome of loss of agitation is not very different from that of loss of cooling.

Heat transfer limitations of the stirred tank

Cooling an exothermic reaction through the jacketed wall of a stirred tank has limitations to consider. Such cooling works on the basis of:

$$Q_{ex} = UA\Delta T \qquad (10.11)$$

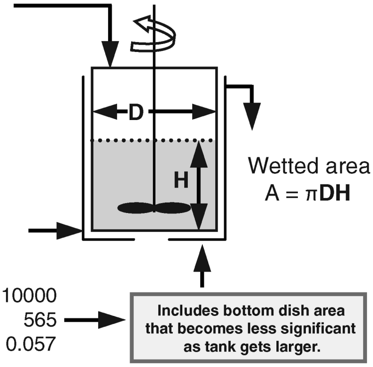
For stirred tanks in particular:

a.- Heat transfer coefficients **U** are low when compared to condensers or heat exchangers

b.- Heat transfer area **A** relative to batch volume decreases with increasing tank size, as set by the cylindrical geometry. Tanks with H/D >1.25 are more difficult to mix well.

Heat transfer surface area per unit of tank operating volume (cylindrical geometry) $\sim \dfrac{\mathbf{4}}{\textbf{Tank diameter}}$

Tank defining dimension for any given cylinder *is in the denominator.*



Includes bottom dish area that becomes less significant as tank gets larger.

For example, Pfaudler RA glass lined reactors have the following jacket areas:

Gallons	300	500	1000	2000	5000	10000
Jacket area, ft^2	50	80	120	190	360	565
Specific area,ft^2/gal.	0.17	0.16	0.12	0,095	0.072	0.057

FIGURE 31 The unfavorable geometry of the stirred tank with respect to heat transfer.

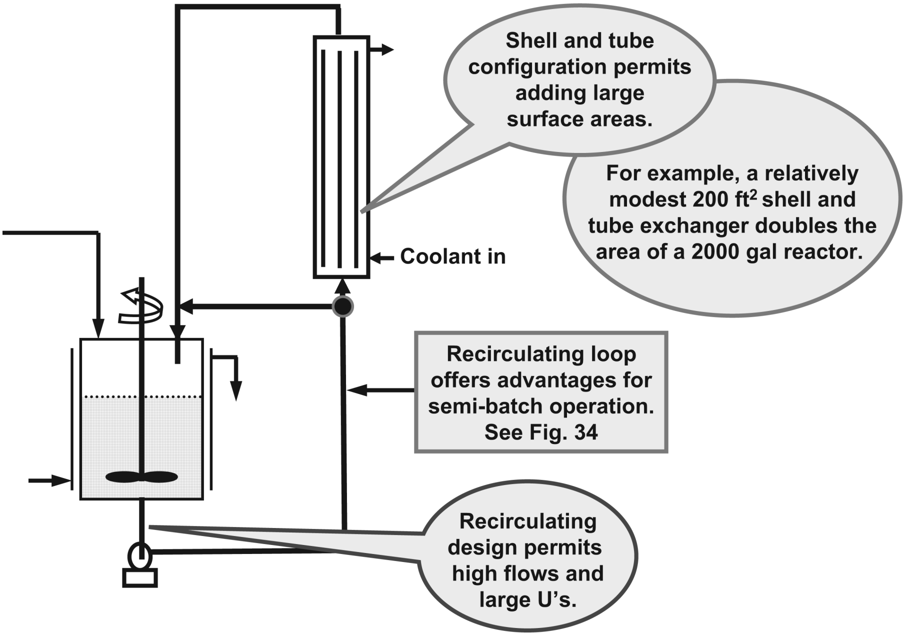
exothermic reactions, a significant reaction exotherm could be handled in the batch mode in two ways:

a. Increase the heat transfer capacity for cooling by providing a much larger surface area than the jacket of a stirred tank offers. The latter is bound by a geometry that reduces the ***specific surface area per unit of reactor volume*** as the reactor is scaled up in diameter, as described in Figure 31. Of the two ways to achieve a much greater surface area than that offered by the jacketed tank, the use of ***an external heat exchanger in a recirculating loop*** is far superior, as discussed in Figure 32.

   Internal cooling coils and tube bundles of various designs [(23), p. 5] are very useful in large tall tanks (i.e., fermentors) because of the significant increase in heat transfer surface area they can add to a jacketed stirred tank. Their use in multiproduct batch chemical processing, as in pharma, is a hardship because of the difficulty in cleaning them to regulatory expectation and, to a lesser extent, by their poor handling of slurries. Such vessels are much better suited for continuous processing with infrequent turnover between different products.

b. Operate the exothermic reaction cycle (with *firm* confidence on our numbers for Q_r) at ***reflux conditions*** as discussed in Figure 33. Evaporative cooling has the formidable advantage of not being limited by heat transfer across a surface area. Synthron was doing this, but neglected the energy balance upon scaling up the batch size and Q_r overwhelmed the Q_{ex} capacity of their condenser.

The stirred tank with an external heat exchanger loop far exceeds the jacketed wall surface area



Shell and tube configuration permits adding large surface areas.

For example, a relatively modest 200 ft^2 shell and tube exchanger doubles the area of a 2000 gal reactor.

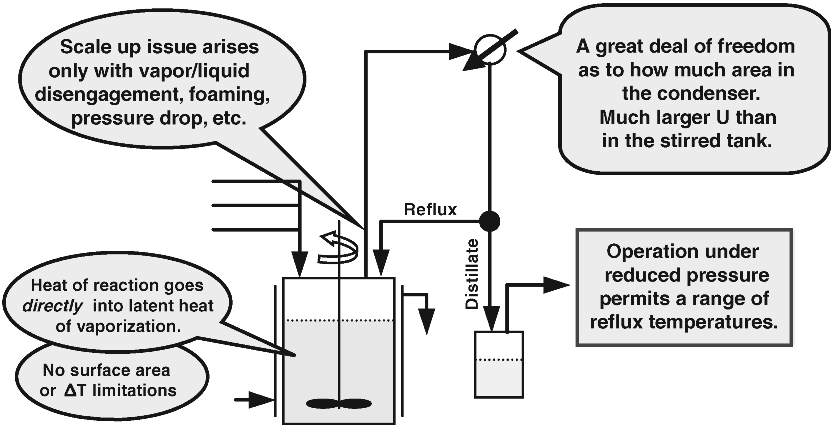
Recirculating loop offers advantages for semi-batch operation. See Fig. 34

Recirculating design permits high flows and large U's.

FIGURE 32 External heat exchanger on a stirred tank reactor.

Evaporative cooling in the stirred tank

Evaporative cooling has significant advantages over cooling through the jacketed wall area, since it transfers the heat load to the more effective condensation of vapor in one of several types of condensers.



Scale up issue arises only with vapor/liquid disengagement, foaming, pressure drop, etc.

A great deal of freedom as to how much area in the condenser. Much larger U than in the stirred tank.

Heat of reaction goes *directly* into latent heat of vaporization.

No surface area or ΔT limitations

Operation under reduced pressure permits a range of reflux temperatures.

FIGURE 33 Evaporation as a way to bypass the heat transfer limitation of the jacketed tank wall.

B. The Semibatch Mode

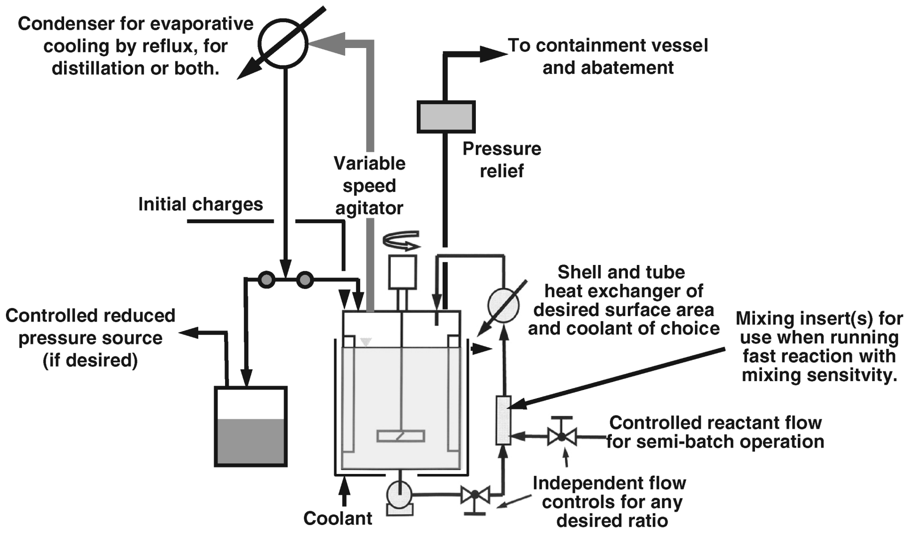
The ***semibatch mode*** of running chemical reactions avoids the problem of having a large store of thermochemical energy in the reaction vessel, as first suggested in Figure 27. This is accomplished by the addition of an indispensable reactant or catalyst over time, which also spreads the removal of the total heat of reaction over a time often of our choice, albeit starting with less that the total jacketed wall area. But combined with either an external heat exchanger (as in Fig. 32) or a reflux operation (as in Fig. 33), the ability of the semibatch mode to handle the large heat of reaction loads is unmatched by any batch mode arrangement and without the risk of the large thermochemical energy store.

> Often enough one finds the term ***semicontinuous*** applied to the semibatch mode, but this is a confusing term for the uninitiated, for the term "continuous" should be reserved for operations at a ***steady state***, which is the most distinctive feature of continuous processing. Indeed, nothing resembling a steady state can be found in the semibatch mode of operation.

As to limitations, the semibatch has the converse of the batch mode limitation—namely, when the selectivity demands of a reaction call for all reactants to be present at the outset to avoid an unfavorable ratio of reactants, the semibatch mode can only reverse the order of addition to obtain the opposite excess. This latter feature, however, is a definite additional advantage of the semibatch mode, for it usually solves the frequent issue of wanting to add A to B rather than B to A. Additionally, the semibatch mode offers considerable variety of reaction control schemes by having the addition rate of an indispensable reactant as a processing variable. This makes it possible to run reactions with control over a greater number of variables—temperature, pressure of a gaseous reactant, pH, conductivity, a particular reactant or product concentration, etc. Finally, the semibatch mode offers the opportunity to interrupt the course of a reaction because of need or advantage, in addition to using the feed rate variable to modulate reaction effects, such as gas release rate, which might be a reaction output handled externally to the reactor.

When it comes to our core issue—safe running of reactions with thermochemical hazards—the semibatch mode is superior in many ways. In this respect, however, we must note that the reaction control via the addition rate of an indispensable reactant (let us call it B) must be mindful of avoiding accumulation of ***unreacted*** B or any high-energy intermediate in the event of ***reactions in series***. For example, the catalytic hydrogenation of nitroaromatics (e.g., Figs. 6 and 10) proceeds in such stages. These, although usually all rapid enough so that the hydrogen rate modulates the whole series, may in some cases (e.g., defective catalyst) allow for hazardous accumulation of the nitroso, hydroxylamine, or other high-energy intermediates [(24), p. 114], all found in the list of the usual high-energy suspects [(15), Table 2.5]. Ideally, semibatch reactions are run to completion of the whole reaction sequence by operating at conditions that ensure high conversion and fast rates, making sure that the total of all heats of reaction is being released as a function of the reactant addition and no significant accumulation of unreacted compounds is taking place. Occasionally, a semibatch reaction is carried out in two distinct stages via the sequential addition of two reactants or a reaction carried out by adding a reactant over time simultaneously with another that might be used to maintain, say, a certain pH or a certain reaction result measurable by means of the proper sensor. This latter

Versatile semi-batch vessel for exothermic and fast mixing sensitive reactions


Condenser for evaporative cooling by reflux, for distillation or both.
To containment vessel and abatement
Pressure relief
Variable speed agitator
Initial charges
Shell and tube heat exchanger of desired surface area and coolant of choice
Mixing insert(s) for use when running fast reaction with mixing sensitvity.
Controlled reduced pressure source (if desired)
Controlled reactant flow for semi-batch operation
Independent flow controls for any desired ratio
Coolant

Not shown to avoid undue clutter: Gas sparger, probes and sampling lines into the vessel, process control loops, etc.

FIGURE 34 The versatile semibatch reactor fully equipped for hazardous exothermic reactions.

feature is another process control advantage of semibatch processing over the batch mode.

Finally, and although suggested in Figure 33, a fuller version of a versatile semibatch reactor is shown in Figure 34, a design that provides high heat transfer rates (heat exchange loop), high intensity mixing of liquid/liquid or gas/liquid streams, evaporative cooling and distillation of a volatile byproduct (an operation sometimes needed to drive a reaction to completion).

C. Continuous Reactors

A great variety of continuous reactors can be found across the chemical industry at large, many quite specific to a task (e.g., gas/solid fluid bed reactors in petrochemicals). In pharma, however, the usual scale of operations, the relatively recent integration of the chemical engineering discipline and tradition have kept continuous reactors as exceptional means of processing. Such reactors, characterized by steady-state operations and throughput of reactant and product streams, have nevertheless a safe niche in thermochemical process safety. Although their appeal has been traditionally their minimal inventory of hazardous in-process materials relative to batch or semibatch processing, continuous reactors have other merits when applied to exothermic reactions and processing high-energy compounds.

Although not much appreciated in pharma, currently so fragmented in its manufacturing and still largely wedded to a five-day-per-week or even two-shift-per-day operation, well-designed processes and plants that run at a steady state enjoy considerable advantage with respect to human error. This stems less from process control and automation than from their operating rhythm and so is much less subject to forgetfulness, improvisations, and the lesser preparedness fostered by being able to put the next batch off to the next shift or fixing a mechanical problem when it might be convenient rather compelling. But again we digress; let us describe the continuous reactors useful in our context of thermochemical safety in pharma.

1. Tubular Reactors

Although design may vary a little, that basic principle is the same throughout—the geometrical advantage of a long and thin cylinder over a stirred tank that rarely operates at H/D >1.25, namely:

a. The relative ease in achieving turbulence and with it the very desirable uniformity of the dwell time (or residence time) of most of the process stream. If there is one attribute of the well-stirred batch mode that one might like is the fact that every volume element shares the same fate during the course of the reaction—if our kinetics model of the reactions is good, its predictions will be good. This attribute—a confidence builder if nothing else—can be pretty well approximated in tubular reactors in turbulent flow, which are not hard to design, build, and operate [(25), chap. 11–16].

b. The much higher surface area available for heat transfer ***per unit of reaction mass volume*** that is afforded by the spaghetti-like geometry of a long and thin tube, which makes it much easier to have a cooling capacity that exceeds the reaction heat release; that is, $Q_{ex} > Q_r$.

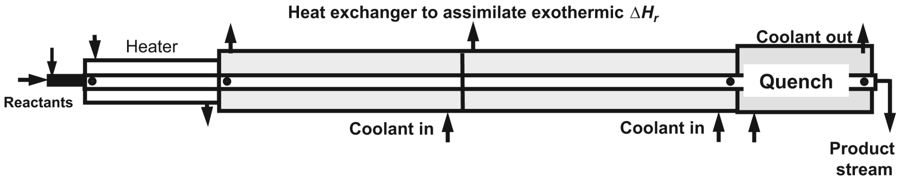
c. For fast and mixing sensitive reactions, the tubular reactor can bring together the reactants far better than the stirred tank batch and comparably to the best design in semibatch reactors (Fig. 34). If semibatch addition is best for reaction selectivity, multiple addition points are easily implemented in the tubular reactor.

d. Finally, for reactions that need to be prompted before they go on their own (as in the case of Morton International), the tubular reactor design can incorporate a preheating section, followed by the cooling section for the exotherm and ending with a quenching section, in which the reaction can be brought to an abrupt slowing down (Fig. 35). These features—the ability to initiate in a quick heat-up, safely assimilate the exotherm, and then terminate just as quickly—are most useful when dealing with reactions that exhibit sharp ascending and descending yield curves as a function of conversion or reaction time at temperature, as in the racemization of the key methyldopa intermediate (26), which was successfully scaled up to ca. 400 mta per single pass reactor. A similar design has been documented for the 400 mta production of nicotinamide from 3-cyanopyridine (27) in a single tubular reactor.

Alas, the pernicious view of continuous reactors being only appropriate at large scale has probably sentenced a good deal of chemistry to less than optimal performance in batch and semibatch reactors. The success of a continuous reactor solving a problem of very fast, mixing sensitive and competitive reactions at a small pharma scale—<40 mta in a multiproduct plant running in

Tubular reactors for exothermic reactions

Tubular reactor for fast, mixing sensitive exothermic reactions in liquid phase - Single tube



Capable of plug flow and high turbulence, with high heat transfer coefficients and high surface to volume ratio. Countercurrent heat exchanger may be divided in several sections to maintain a large ΔT for the heat exchange (only two sections are shown above). For greater surface area to volume ratio when heats of reaction are large or process temperature needs to be kept low, the well mixed feed stream may be divided into a number of smaller diameter tubes in a shell and tube configuration, but designed to ensure even flow distribution among the tubes for uniformity of residence time.

The preheater section is used only when needed for reaction initiation and the quench section may be used with much colder coolant when tight control of residence time is desired via abrupt, rapid cool down. Residence time is varied as needed by flow rat.

In the extreme, the multi-tube configuration is the conceptual basis of the so-called microreactors based on channels of very small dimensions rather than tubes.

FIGURE 35 Tubular reactors beat the odds of the cylindrical geometry and permit plug flow in addition to being far better suited for mixing sensitive reactions.

campaigns—was realized by simply ***inserting*** a brief continuous reaction step within a batch and semibatch processing sequence (28), a method that that particular process team has implemented multiple times (29).

2. The Continuous Stirred Tank Reactor

The CSTR is a stirred tank reactor operating at a steady state; input streams enter, chemical reactions and whatever else happens steadily, output streams leave, all process variables are within a narrow range of their assigned control values, and the contents of the process stream in the tank are well mixed, uniform throughout. Indeed, the CSTR is one of the ideal reactor models, whereas the plug flow reactor (PFR) is at the other extreme, and all other models fall in between.

Unlike the tubular reactor, which approaches the PFR model, the CSTR operates at a lower conversion for a given residence time of the process stream, but this key difference with the PFR can be reduced by operating more than one CSTR in series, all tanks being of equal size. Indeed, the more tanks in series, the closer the reactions and the residence time distribution of the process stream approaching the PFR performance. For our purposes herein, it suffices to say that for any given conversion of reactants to products, a single CSTR needs to hold a greater amount of process stream than the PFR, and the higher the conversion, the greater the difference in the operating volume between the two reactors—the single CSTR needs to be much larger. This difference can be reduced by operating several CSTRs in series (a CSTR cascade), although approaching the PFR performance at high conversion requires a good number of equally sized CSTRs. We will leave the topic here, closing with the observation that only for very fast reactions does the CSTR cascade become practical as a means to high reactant conversion and referring the reader to Levenspiel's chapter 6 in reference (25).

Then, why CSTRs for a thermochemically hazardous reaction? The answer is relatively simple, for as long as one does not insist in matching the PFR or the batch reactor in conversion performance, CSTRs hold a much smaller amount of thermochemical energy in a single vessel and operate at a more favorable heat transfer area to volume ratio than batch reactors—thus the CSTR having some utility in very hazardous processing (e.g., the nitration of glycerine), particularly if the process permits facile recycle of unreacted starting material and there is need for intense mixing of more than one liquid phase ***during*** the course of the reaction (a failing of the tubular reactor).

Figure 36 depicts a CSTR equipped with internal cooling as well as a jacket—the internal cooling system that would clutter the diagram least was chosen from among the offerings described (23). Indeed, there is also a niche in high-energy reaction processing for a well-designed CSTR cascade (e.g., running relatively fast nitrations, sulfonations, and the like, where multiple liquid phases need to be kept well distributed with each other under high–mass transfer conditions) (Fig. 36). Let us recall the compelling argument for operating such high-energy systems at a minimum inventory of material reacting exothermically or prone to exothermic decomposition (30). One can only assume that many people in the former Union Carbide organization, particularly those that designed the process and pesticides plant at Bhopal, wished they had pursued a

Continuous stirred tank reactor (CSTR)

This CSTR is provided with an internal cooling system as well as its jacket. A ring of vertical tubes is depicted. Impeller diameter has been reduced for the sake of this depiction Cooling tubes make baffling unnecessary.

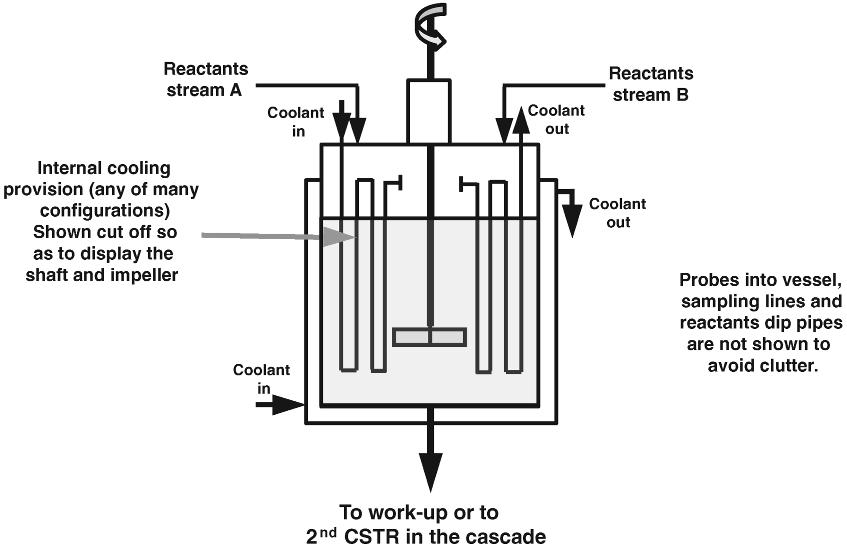

Reactants stream A
Reactants stream B
Coolant in
Coolant out
Internal cooling provision (any of many configurations) Shown cut off so as to display the shaft and impeller
Coolant out
Probes into vessel, sampling lines and reactants dip pipes are not shown to avoid clutter.
Coolant in
To work-up or to 2nd CSTR in the cascade

FIGURE 36 The well-equipped CSTR occupies a niche in exothermic reaction processing.

continuous process for the preparation and immediate use of methyl isocyanate. Instead, the processing was provided with a storage capacity of up to 45 tons of the compound in each of three storage tanks. Tragically, it appears that a process not requiring storage of methyl isocyanate was available (4).

VII. THERMOCHEMICAL HAZARD AVOIDANCE, PREVENTION, AND RISK REDUCTION

A. Hazards Upon Processing Abnormalities or Change

Several of the references at the end of this chapter include brief discussions of actual thermochemical accidents (1–4,15,16,17,18), and one is struck by how many of the cases could be attributed, in part at least, to processing abnormalities, many of which were mishandled, and to start-ups and changes in processing that were ill considered or poorly executed. Obviously, the role of a rigorous process change management system, with accountable ownership in the organization, is indispensable to safe thermochemical processing, and the reader is referred to chapter 3 for guidance and specifics on the subject. Also of note is the frequency of "Friday night" decisions that were troublesome over the weekend, which reinforces the extra alertness needed when the processing does not have a good operating rhythm or the good rhythm is interrupted.

B. The Safe Process Envelope

The concept of the safe process envelope is simple: bring to bear all the process know-how and necessary design skills (not just those that are conveniently available) to define the boundaries of the process (***as implemented at the plant scale***) with a focus on thermochemical safety ***within*** the overall process safety effort. Initial boundaries need to be defined from the hazards assessment—the starting envelope (Fig. 19, chap. 2)—and then ***redefined*** as the development and process design interaction starts ***as early as possible*** (see Fig. 1, chap. 3) so that the implemented project is based on the ***contoured*** safe process envelope (see Fig. 21, chap. 3). Indeed, chapter 3 covers this ground extensively and deeply, and repetition herein is not warranted.

C. The Role of Process Design Based on the Hazard Assessment

The meaning of the above heading can be stated briefly: the hazards assessment is considerably richer than the accumulation of test results, for it cannot be completed if the process design scenarios are not blended in with the risk assessment of the design solutions to the hazards being accepted in principle, some of which may have to be rejected upon assessing the risks. Once more, chapter 3 delves into the process design role with respect to assessing hazards and their risks for the implementation scenarios, and Figure 20 in that chapter depicts the working mechanics at hand.

D. Formal Hazards Assessment of Process Operations

There are formal methods of ***operational*** hazards assessment (1,20,31,32,33), and it would be beyond the scope of this chapter to describe them—thus our deferring to the broader scope of chapter 11. We will just make the point that the technology transfer through process design and start-up of first manufacture must embrace the operational hazards and risk assessments.

E. The Outsourcing Environment—Hazards and Risks

As the outsourcing business model of pharma manufacturing surges forward on a broad front (35), the appreciation of its hazards and risks must be foremost in the minds of those executing outsourced operations—both the client that needs the bulk drug and the supplier that needs the business. To this author, thermochemical process safety in the outsourcing mode of securing the supply of new bulk drugs is pregnant with hazards and risks (34), an issue that has been recognized by the American Institute of Chemical Engineers through the publication of a thoughtful "how to" document (34), which should be at the desk of everyone involved.

The situation is particularly hazardous when there is a significant transfer of process technology from the owner of the drug and its NDA to one or more contract suppliers, during which thermochemical process safety often does not get the attention it deserves and the ***relevant know-how disperses***. Worst of all is the case of the ***virtual*** pharma organization that licenses a drug candidate with an incomplete process package and then needs the licensor—who has whatever process know-how exists—to go and help the supplier, who often has too high an opinion of its own skills and insists in putting its imprint on the process or shoehorning it into its plant. To his good fortune, the author had nothing but good experiences during his corporate career, due to the deep commitment of the client to the tech transfer and the good choices of conscientious and capable suppliers. Alas, that was long ago, and such have not been the author's observations in his postcorporate career, with thermochemical process safety often getting short shrift in many of the cases observed.

VIII. IN CLOSING

The practice of thermochemical process safety—as one of the three pillars of chemical processing—is an activity based on skills, discipline, and focused attention at all levels and on both sides of every organizational boundary—the internal ones within a pharma organization and those between client and supplier. It is not a field to dabble in, for to practice in it there has to be a serious commitment of physical and human resources. And even those who choose to contract out hazard and risk assessment work need to have skilled people who can stay on top of the contracted work and see it applied properly wherever the implementation takes place.

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11 Design and Operating Practices for Safety

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I. INTRODUCTION

Many hazardous chemicals are used in the production of active pharmaceutical ingredients (APIs). These chemicals may be flammable/combustible liquids, toxic gases, water-reactive chemicals, and cyanides, to mention several types.

In addition, some final APIs may be health hazardous to operators working with them; for example, they may be carcinogenic, mutagenic, or teratogenic, and have to be contained to prevent them from coming in contact with the operators. These hazardous chemicals can result in fires, explosions, and releases of toxic gases or health-hazardous APIs if they are not controlled.

A number of technical organizations in the United States publish standards and guidelines for the safe design and operation of chemical and pharmaceutical plants. Among these organizations are American Institute of Chemical Engineers/ Center for Chemical Process Safety (AIChE/CCPS) (www.aiche.org), American Petroleum Institute (API) (www.api.org), National Fire Protection Association (NFPA) (www.nfpa.org), FM Global (www.fmglobal.com), and International Society for Pharmaceutical Engineering (ISPE) (www.ispe.org).

In addition, all companies must comply with the regulations issued by the Occupational Safety and Health Administration (OSHA) (www.osha.gov) and the Environmental Protection Agency (EPA) (www.epa.gov).

In Europe, the International Standards Organization (ISO) (www.iso.org) and the Comité Européen de Normalisation (CEN) (www.cen.eu) publish standards and guidelines similar to those published by the U.S. companies mentioned earlier. Also, the U.K. Health and Safety Executive has published many documents on process safety and loss prevention (www.hse.gov.uk).

On July 1, 2003, the ATEX Directive became mandatory in Europe and governed by European law for all electrical and mechanical equipment used in potentially explosive atmospheres (as are often found in chemical and pharmaceutical plants). ATEX is the name commonly given to the framework for controlling explosive atmospheres in the workplace and the standards for equipment and protective systems used in them. More information on ATEX can be found on the U.K. Health and Safety Executive Web site.

This chapter discusses design and operating practices that can be used to eliminate or minimize the hazards mentioned previously so that the plant is operated in a safe manner, protecting the process equipment and operators.

II. FLAMMABLE/COMBUSTIBLE LIQUIDS STORAGE AND HANDLING

A. Storage

1. Introduction

Flammable and combustible liquids are stored in tanks in tank farms or in "day" tanks in buildings. Tanks in these farms are usually vertical atmospheric- or low-pressure tanks of the API type (fixed or floating roof) for large volumes, or vertical or horizontal tanks of the ASME type for smaller volumes (usually up to about 50,000 gal). These ASME-type tanks are designed for about 14.5 psig so that they are not considered to be pressure vessels under section VIII of the ASME Boiler and Pressure Vessel Code, and do not require a code stamp or the use of an ASME-certified welder to make repairs. In pharmaceutical plants, "day" tanks are supported on legs so that the area under them can be easily washed down and cleaned.

NFPA 30 (1) defines a flammable liquid as one that has a closed-cup flash point below 100°F (37.8°C) and a Reid vapor pressure that does not exceed an absolute pressure of 40 psi (276 kPa) at 100°F, and a combustible liquid as one that has a closed-cup flash point above 100°F. In addition, flammable liquids are classified as class IA, IB, and IC, as follows:

a. Class IA liquid—any liquid that has a flash point below 73°F (22.8°C) and a boiling point below 100°F (37.8°C)
b. Class IB liquid—any liquid that has a flash point below 73°F and a boiling point at or above 100°F
c. Class IC liquid—any liquid that has a flash point at or above 73°F, but below 100°F

Classifications for combustible liquids (class II and class III) are also defined in NFPA 30.

The liquid class affects such design considerations as location of tanks with respect to other tanks and equipment, property lines, and important plant buildings; normal and emergency venting; and requirements for conservation vents and/or flame arresters. Some of these design considerations and practices are discussed in the following sections.

Tank location and layout. Criteria for tank farm tank locations and installation are given in chapter 22 of NFPA 30. Design criteria are also presented for diking in chapter 22. For "day" tanks inside of buildings, distances between tanks and other equipment are usually based on the area needed for operator access and maintenance work.

Tank filling. Storage tanks in tank farms are quite often filled from tanker trucks or railcars. Before the transfer of liquid into the storage tank is begun, all equipment in the transfer system (truck or railcar, storage tank, and piping) must be properly bonded and grounded. Information on this can be found in NFPA 77 (2) and API RP 2003 (3). The bonding and grounding should be checked for electrical continuity before starting liquid transfer by using commercially available equipment for this.

Fill pipes that enter the top of a storage tank should terminate within 6 in. (150 mm) of the bottom of the tank. They should be installed or arranged so that vibration is minimized.

Day tanks inside buildings are usually filled from tanker trucks or drums. Bonding and grounding requirements and fill pipe design and installation should be the same as for tank farm tanks.

All storage tanks containing flammable or combustible liquids should be provided with overfill protection. The tank should be equipped with a high-level detection instrument (often a capacitance probe) that is independent of the tank's normal level indication instrumentation, and is interlocked to close an open-shut valve in the fill line. The high-level detector can also be interlocked to shut down a pump that feeds liquid to the tank, and equipped with alarms that are located where personnel who are on duty throughout liquid transfer can arrange to shut down the pump or divert the flow to another item of equipment in accordance with established procedures. Figure 1 is a schematic of a typical overflow protection system.

Normal and emergency relief venting. Normal venting is provided to permit the intake and discharge of air during filling and emptying operations and to permit expansion and contraction of vapor due to temperature changes.

Criteria for normal venting of tanks and vent sizing are given in chapter 21 of NFPA 30. This chapter stipulates the following:

a. Provide normally closed venting devices, that is, conservation vents, on tanks storing class IA liquids.
b. Provide normally closed venting devices, that is, conservation vents, or with an approved (listed) flame arrester, on tanks storing class IB or class IC liquids.

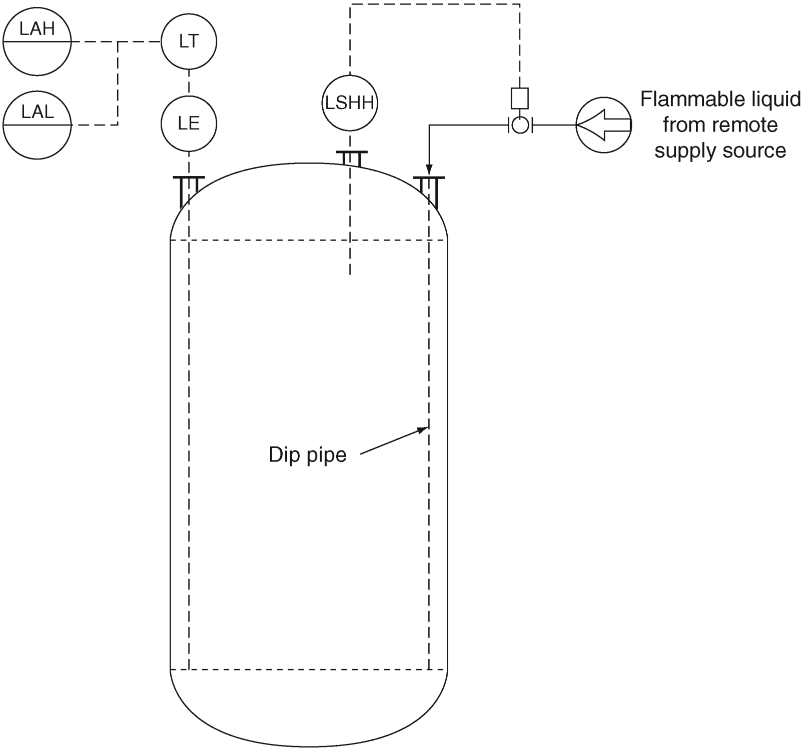

FIGURE 1 Level overfill protection.

Chapter 21 of NFPA 30 recommends that normal vents be sized using the equations in API Standard 2000 (2), or alternatively, the vent shall be at least as large as the largest filling or withdrawal connection, but in no case shall it be less than 1.25-in. (32-mm) nominal inside diameter.

In addition, NFPA 30 states that for tanks equipped with vents that permit pressures to exceed 2.5 psig and for low-pressure tanks and for pressure vessels, the outlet of all vents and vent drains shall be arranged in a manner that prevents localized overheating of, or flame impingement on, any part of the tank if vapors from the vents are ignited. This means that "goosenecks" should not be located so that vapors from the vent will impinge on the roof or sidewalls of the tank.

Criteria for emergency venting and vent sizing are given in chapter 22 of NFPA 30. Tables are presented containing vent sizes as a function of tank volumes.

Storage tanks (tank farm or "day" tanks) should be provided with inert gas blanketing where the tanks store liquid with a flash point less than 100°F (4).

Manifolded vent systems. Many states in the United States require that vents from tanks containing volatile organic compounds (VOCs) be manifolded to collect the vent vapors for pollution control purposes and these vapors then sent to a control device such as a flare, a thermal or catalytic oxidizer, or a scrubber.

For manifolded vent systems, the following safety measures should be followed (4):

- Do not manifold vent collection systems of tanks containing incompatible chemicals.
- Do not manifold vent pipes from tanks containing liquids with flash points below or equal to 100°F with tanks containing liquids with flash points above 100°F.
- Protect low-pressure storage tanks interconnected with fume recovery or collection systems against explosion propagation if they normally contain ignitable mixtures and ignition sources (e.g., spontaneous heating) could be or are normally present (continuous flames as in flares, thermal oxidizers, etc.), by one of the following methods:
  a. Oxidant concentration reduction (e.g., inerting or purging). This method should not be used if open manhole activities, such as sampling and liquid or solids addition, are performed. Inerted systems should be monitored by oxygen analyzers, with high O_2 alarms, and a backup inert gas (usually nitrogen) supply (e.g., nitrogen cylinders) hooked up to the manifold and automatically activated by the high-level oxygen concentration in the analyzer.
  b. Combustible vapor concentration reduction (e.g., ventilation). This method is not often used in industry.
  c. Explosion isolation (detonation arresters). This method is widely used in the chemical process industries. Where an explosion isolation system is used, the detonation arresters must be approved by testing by accepted test methods. In this system, there must be a detonation arrester at each tank vent nozzle interconnected with the vent manifold and a detonation flame arrester at the end of the manifold immediately upstream of the

feed nozzle of any vapor control equipment, such as a thermal oxidizer or a scrubber (Fig. 2). Detonation arresters should be provided with temperature sensors on each side and as close as possible to the face of the arresting element. Instrument the arrester to automatically close valves or initiate other actions that will eliminate the possibility of a stabilized flame burning on the arrester element. Do not locate the sensor in a thermowell that will delay its response. If the sensor is to be a metal-sheathed thermocouple, it must be of small diameter, for example, ¼ in. (6 mm), and must be inserted through a suitable packing gland. (Note: Detonation arresters may not be suitable in systems where powders are added to the tank on a regular basis as the arresters could become plugged and fail to handle normal in-and-out breathing.)

B. Handling

1. Piping and Valves

For flammable and combustible liquids, piping, valves, and fittings should be metallic, for example, carbon steel, stainless steel, or other suitable alloy chosen for corrosion resistance. Avoid materials such as cast irons, high-silicon irons, plastics (thermoset and thermoplastic), glass, and aluminum, as these have potential for failure (low impact strength, low-pressure ratings, low resistance to thermal shock, and low melting point).

It is good engineering practice to provide block valves in all liquid lines entering and leaving tanks and process equipment to be able to stop the liquid flow during a fire and to limit the quantity of liquid spilled in the event of accidental release. The valves should be located so that they are easily reached, or provided with remote activation to close them. Outlet (withdrawal) nozzles

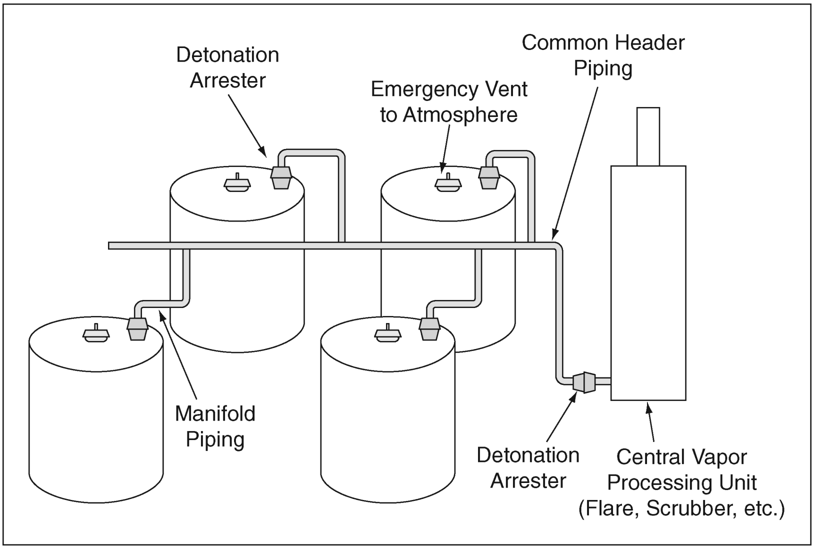
Detonation Arrester
Common Header Piping
Emergency Vent to Atmosphere
Manifold Piping
Detonation Arrester
Central Vapor Processing Unit (Flare, Scrubber, etc.)

FIGURE 2 Manifolded tanks.

on storage tanks of capacities exceeding 10,000 gal (28 m^3) should be provided with shutoff valves that are operable from a remote location in case of a spill or fire in the tank farm. Where there is a possibility of having a fire near a tank, consideration should be given to using fire-safe valves.

Provide a liquid-tight closure, such as a valve, plug, or blind, or a combination of these, on connections below the liquid level through which liquid does not normally flow (e.g., a drain nozzle).

2. Pumps

Many types of pumps are used for transferring flammable and combustible liquids, such as centrifugal and positive-displacement (rotary, reciprocating, and diaphragm) pumps.

In recent years, sealless pumps are being used more frequently for highly flammable or toxic liquids. Both centrifugal and rotary pumps are available in sealless designs.

Centrifugal pumps. Centrifugal pumps are the most commonly used type of pump in chemical and pharmaceutical plants. For flammable and combustible liquids, they should be provided with double inside mechanical seals or tandem mechanical seals with a compatible buffer liquid between the seals. The following hazards can occur with centrifugal pumps:

- Mechanical seal failure
- Reduced or low flow
- Overpressurization from thermal expansion
- High temperatures
- Cavitation

The following preventive and protective measures should be provided for the above-mentioned hazards:

Mechanical seal failure. Mechanical seal failure can occur due to loss of buffer fluid through the seal. This can be avoided by providing a seal system that consists of a circulating pressurized reservoir with an internal cooling coil and low-level alarm. Figure 3 is a schematic of such a system.

In recent years, gas-barrier seals have been used in place of buffer-liquid seals in many applications, and they warrant serious consideration.

Reduced or low flow. Operation of centrifugal pumps at severely reduced flow or at shutoff should be avoided, as this can create unstable flow conditions and cause excessive vibration and damage to pumps, drivers, couplings, gears, piping, and adjacent equipment. To prevent this from happening, centrifugal pumps should be provided with a minimum-flow recirculation (bypass) line from the pump discharge side of the pump, located upstream of the block and check valves. This bypass line should preferably be routed back to the pump supply vessel if it is an adequate "heat sink." Otherwise, the minimum-flow bypass line should be routed through an external cooler before returning to the supply vessel or pump suction line.

There are a number of methods available to detect low-flow conditions, including the use of a flow sensor in the pump suction line, an ammeter to

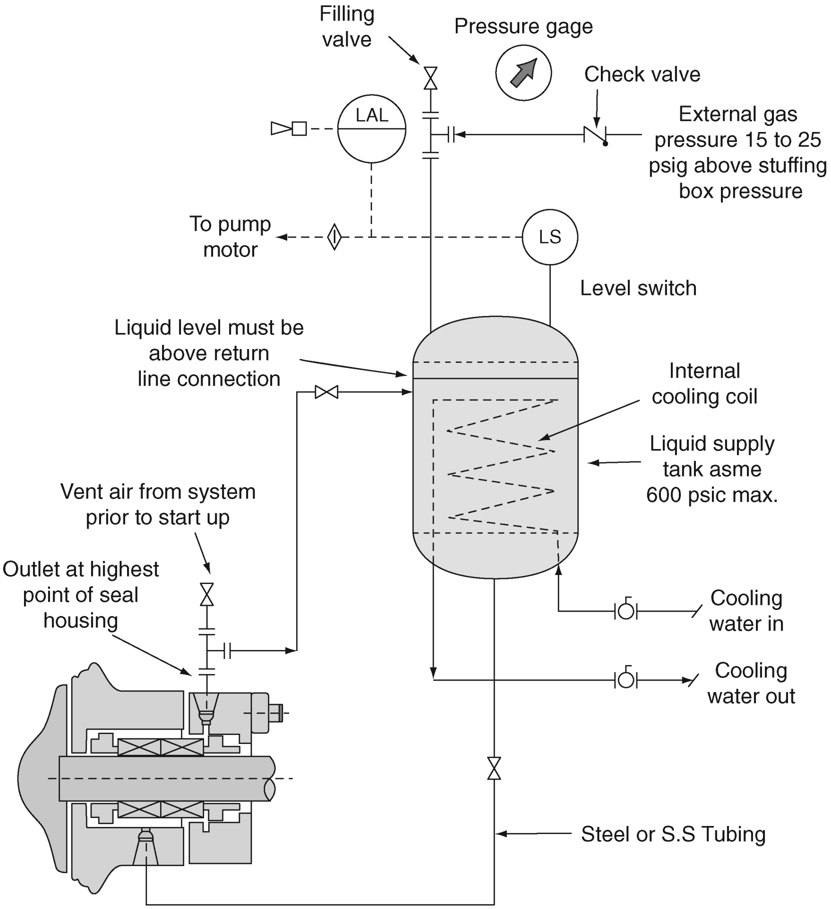
Filling valve
Pressure gage
Check valve
LAL
External gas pressure 15 to 25 psig above stuffing box pressure
To pump motor
LS
Level switch
Liquid level must be above return line connection
Internal cooling coil
Liquid supply tank asme 600 psic max.
Vent air from system prior to start up
Outlet at highest point of seal housing
Cooling water in
Cooling water out
Steel or S.S Tubing

FIGURE 3 Mechanical seal buffer liquid system with pressurized external reservoir.

measure the amperage draw of the motor, and a power monitor to measure the motor horsepower. These sensors can be interlocked with the pump motor to shut it down upon detection of reduced or low flow.

Overpressurization from thermal expansion. Overpressurization protection from thermal expansion is needed for centrifugal pumps that can be valved in when there is a remote start-up capability or when both the suction and the discharge lines have automatic closing valves.

Overpressurization protection is also needed if the pump shutoff head exceeds the pressure rating of the system piping. Protection is usually provided by a pressure relief valve from which the discharge is directed back to the pump supply vessel.

High temperature. High temperature can occur in a liquid when a pump operates against a closed valve, which is known as "deadheading." This is a very dangerous situation for some liquids that can decompose when subjected to high temperatures and, subsequently, may lead to an explosion within the pump. When pumping such high-hazard liquids, a temperature sensor should be installed in the pump casing that will alarm and shut the motor down before a thermal runaway reaction can occur.

Cavitation. Cavitation can cause pressure variation, shaft deflection, vibration, or mechanical shock that will damage mechanical seal components. This problem can be avoided by proper design of supply vessels and suction piping systems. It can usually be avoided by ensuring that the pump has adequate net-positive suction head (NPSH) and that entrained gases are avoided. NPSH requirements should always be obtained from the pump manufacturer.

Backflow can occur in a centrifugal pump system when the motor (or other driver) is stopped, either intentionally or accidentally. This can result in backflow of liquid through the pump to the suction vessel and, possibly, vessel overflow. It may also result in reverse rotation of a non-running installed standby spare pump, which could damage it. To avoid or limit backflow, a check valve should be installed in the pump discharge line. For highly flammable liquids, it may be desirable to install two check valves in series. Alternatively, a fast-acting open-shut valve, activated by a low-pressure sensor in the discharge line that will shut the valve tightly, can be used. When check valves or fast-acting valves are installed in the discharge line of a pump, it may be necessary to establish a way to prevent hydraulic hammer.

Positive-displacement pumps. Most positive-displacement pumps require a pressure relief device to protect against overpressure that can be caused by a closed discharge valve or restricted discharge line. External pressure relief valves are typically used because they are easy to see when open, can easily be adjusted to any set pressure, and remain open only long enough to relieve pressure, thereby reducing process liquid loss. Some positive-displacement pumps are sometimes provided with an internal relief valve, but this is a drawback because an internal relief valve does not dissipate heat. Even if a pump comes equipped with an internal relief valve, it is strongly recommended that an external relief valve also be installed. The external relief valve should be located as close as possible to the pump discharge nozzle and before any block valve.

Diaphragm pumps are used for many hazardous-liquid (flammable and toxic) handling applications because they have no mechanical seals or packing and are essentially sealless pumps. They can be either motor driven or air operated and can have either single or double diaphragms.

Since single-diaphragm pumps can leak if the diaphragm fails, double-diaphragm pumps are recommended for highly hazardous liquids. The space between the two diaphragms can be fitted with any of several leak-detection sensors (using a pH, liquid conductivity, or pressure sensor), which will detect a leak in the inner diaphragm and set off an alarm.

Air-operated diaphragm pumps usually vibrate because of their mode of operation. Therefore, the suction and discharge piping should not be hard piped to the pump nozzles, but should have flexible hose piping. The hoses should be able to move enough so that the movement of the pump caused by vibrations is offset. If the hoses are not long enough to provide movement, they become

TABLE 1 A Comparison of Sealless Pumps

Selection criteria	Magnetic coupling	Canned motor pump
How safe is the unit during failure?	Restricted: unit has only one sealed liner, if liner ruptures, the fluid escapes into the atmosphere	Extended: two boundaries exist the can and the motor housing; if the can ruptures, the motor housing takes over as a gas-fight barrier
Applications	Restricted: limited by the rotating mass and construction size	Extended
Viscosity range	Restricted: an increase in viscosity establishes relative limitations	Extended: the fluid is warmed going through the motor section allowing the pumping of higher viscosity material
Total viscosity	Equal	Equal
Temperature limitation	Restricted: limited to applications between 100°F and 754°F	Extended: can be used at temperatures between –200 and 1000°F
Temperature control	Restricted: only the pump can be insulated and traced	Extended: both the pump and the motor can be insulated and traced
Maximum operating pressures	Restricted: the can thickness limits the maximum pressure	Extended: the achievable working pressures are independent of the can thickness because support can be furnished outside of the gap, the current limit for system pressure is approximately 17,000 psi
NPSH required	Better: the lower heat input to the recirculation stream assures better NPSH characteristics	Worse
Explosion protection due to leakage	Restricted: see comment under row 1	Extended
Repair of motor	Better: uses a standard motor	Worse
Sensitivity of solids	Worse: units are more sensitive to solids, especially when ferrous particles are in the fluid	Better: units are available with slurry designs, which isolate the motor section from the pumped fluids
Starting problems	Can exist extreme care must be taken in applying the torque requirements to these units	Not normally
Noise levels	Greater: much higher levels due to the fan on the motor and the additional bearings in the coupling	Lower: these pumps are especially quiet; cooling, coupling, and bearing noises do not exist
Overall length	Greater	Less
Flexibility of installation	Restricted	Extended: units can be installed either vertically or horizontally in generally a much smaller space
Interchangeability with standard chemical pumps	Depends on individual manufacturer	Depends on individual manufacturer
Electrical installation	Depends on individual manufacture	Depends on individual manufacturer
Cost of manufacture	Greater	Less
Foundation	Required	Not required
Coupling	Yes	No
Coupling guard	Yes	No
Coupling alignment	Yes	No
Cost of repair	Less: the repair of the pump and the coupling can usually be accomplished by normal maintenance mechanics	More: repair requires mechanical as well as electrical knowledge
Bearing wear monitors	Not normally available	Widely used

Abbreviation: NPSH, net positive suction head.

comparable to hard piping and can cause damage to the pump. The hoses should be metal-braided type rather than rubber hoses.

Sealless pumps. Two kinds of sealless pumps are available: canned-motor and magnetic drive types. The difference between these two types lies in how the rotor is driven. These two types and their differences are described by Grossel (5). Table 1 is a comparison of sealless pumps. Although sealless pumps do not have mechanical seals that can fail and release liquid, they have their own safety considerations. Most failures of sealless pumps are caused by running them dry and damaging the bearings. A low-boiling liquid may flash and the sleeve bearing can run dry. Also, solids may abrade the bearing of magnetic drive pumps or may plug small ports in the can area. A variety of monitoring devices are available to detect sealless pump problems prior to pump failure. Table 2 lists causes and effects of sealless pump failures and appropriate failure-detection monitors.

TABLE 2 Causes and Effects of Sealless Pump Failures with Appropriate Failure Detection Monitors

Cause	Effects	Results	Type of monitor available
Dry-running (worst possible condition—no flow in any part of the pump)	Rapid temperature rise of containment shell Decrease in horsepower Accelerated bearing wear	Ultimate, if not immediate failure	Flow switch Pressure switch Power/current sensor Temperature monitor
Closed discharge valve (no discharge flow, but fluid circulates through shell area)	Temperature of containment shell fluid will rise Decrease in horsepower Highest discharge pressure	Failure will depend on length of time pump is operating in given condition	Flow switch Power/current sensor Temperature monitor
Decoupled (inner magnet is not rotating no flow but pump is wet)	Temperature of containment shell will rise Decrease in horsepower	Failure will depend on length of time pump is operating in given condition	Flow switch Power/current sensor
Worn sleeve bearings/shaft inside pump	Wear has reached maximum, causing inner magnet to offset and rupture containment shell, and impeller to contact volute	Failure (possible leakage)	Bearing wear monitor Vibration monitor
Worn roller/ball bearings (in power frame)	Outer magnet is offset and contacts containment shell (possible rupture) or other part of the pump housing	Leakage through containment shell	Temperature monitor (based on friction heal) Vibration monitor

III. TOXIC GAS STORAGE AND HANDLING

A number of toxic gases are used in the production of APIs. Phosgene is one of the most widely used toxic gases. This section discusses its storage and handling, which is representative of other toxic gases.

A. Storage

Phosgene is shipped as liquefied compressed gas in two types of containers: 120-lb and 1-ton cylinders. These are the weights of phosgene in the containers.

Phosgene containers should be stored outdoors or in a well-ventilated, separate, noncombustible building away from heavily trafficked areas and emergency exits. The storage area must be well ventilated because phosgene is heavier than air and vapors will fall to the floor if a leak occurs. Phosgene must be stored away from other chemicals that are not compatible with it and from contact with water, moisture, or steam since violent reactions occur, if contact occurs.

It should also be kept away from sources of heat such as flames and heating ducts and sources of excessive corrosion.

Keep containers away from operating equipment and in a location where they are accessible for inspection. Cylinders must be protected from physical damage. Cylinders must be stored upright and firmly secured to prevent falling or being knocked over. Do not allow the temperature of the room or area where cylinders are stored to exceed 130°F (54°C). Empty containers should be clearly identified and stored separately from full cylinders with the same precautions. Containers, both full and empty, should be stored with all valves closed and the outlet valve caps and bonnets in place. Use a "first-in/first-out" inventory system to prevent full cylinders being stored for excessive periods of time. Store 120-lb cylinders in a vertical position and 1-ton tanks in a horizontal position.

If stored outdoors, the container should be protected from direct sunlight and not be placed on the ground so as to protect the bottom from corrosion.

For additional information on phosgene cylinder or tank storage, consult Compressed Gas Association Pamphlet P-1 (6).

B. Handling

A description of a system for the unloading of phosgene from 1-ton cylinders is given by Alspach and Bianchi (7). The phosgene-handling facility is in a separate building located approximately 100 ft from all other buildings. The building has an enclosure with a glove box arrangement, with rubber gloves, through which the operator makes connections to the cylinder.

Two cylinders are placed on separate scales and the operating ends of the cylinders protrude into an enclosure located in the front wall of the building. The cylinders are connected to piping by flexible metal hoses. High-pressure nitrogen is used to push the phosgene from the cylinders through the feed piping to the process reaction area. Connections are made to the cylinder by the operator going to outside of the building and reaching through the inner panel (transparent plastic) and using the gloves. This work is the most hazardous part of the phosgene-handling operation, and the glove box area is constantly monitored (with phosgene levels recorded) for leaks. An alarm is set to sound at 0.1 ppm (which was the threshold limit value (TLV) in effect at that time). The

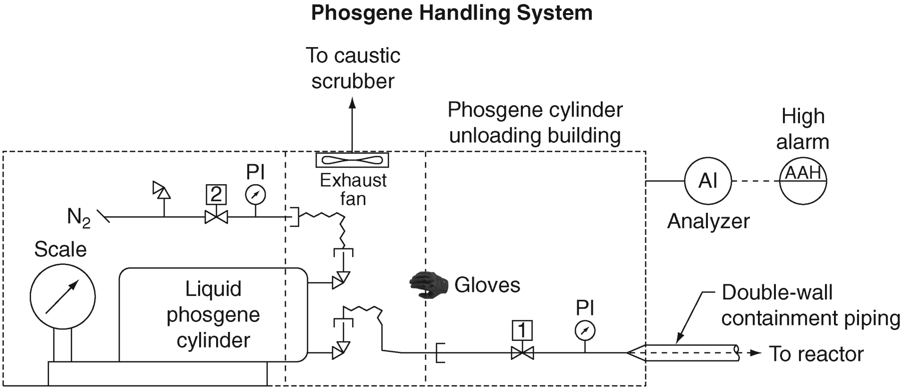
Phosgene Handling System

FIGURE 4 Unloading facility for 1-ton phosgene cylinders.

reason for the outside operation is that, in the event of an emergency (leak), the operator may be reached without anyone entering the building or going into the immediate vicinity of the cylinder. Valve handles extend through the transparent panel, enabling the operator to open or close valves for the flow of phosgene. The enclosure is continually vented by an exhaust fan to a caustic scrubber while any personnel are in the area of the building. The scrubber exhaust is continuously monitored (and recorded) for phosgene. An effluent level of 2 ppm triggers the area evacuation alarm system.

The phosgene-handling building is protected in front of the enclosure and at the doors with infrared personnel detectors. These devices detect unauthorized personnel at the building and, consequently, sound an alarm in the manufacturing area.

To contain a liquid spill from a cylinder, the building floor drains are connected to an underground tank for neutralization with 12% caustic soda. The building floor is provided with a lip to contain a spill.

The feed piping is of double-wall construction made of schedule 80, welded, 316 stainless steel. The annular volume of the double-wall feed (transfer) piping is monitored for phosgene leaks by continuously venting this volume into a solution of Congo Red.

Operators wear air supply systems during both handling cylinders within the building and connecting or disconnecting cylinders at the enclosure. The air is supplied from portable air cylinders, located adjacent to the building, through retractable air hoses. This system permits free movement of the operators.

Figure 4 is a schematic of the 1-ton phosgene cylinder handling (unloading) building and its construction and components.

IV. WATER-REACTIVE CHEMICALS

Two widely used water-reactive chemicals used in the manufacture of APIs are magnesium and sodium. Magnesium is used for the preparation of Grignard reagents, and sodium is used as a reducing agent in many reactions. Grignard reagents are formed as a result of a reaction between metallic magnesium and an organic halide (chloride, bromide, or iodide) in the presence of an ether solvent and in the absence of water. They can also be purchased commercially in 55-gal drums already prepared or can be prepared on a plant site in a process from magnesium turnings or chips.

This section discusses storage and handling practices for the safe use of magnesium in preparing Grignard reagents, the use of Grignard reagents in a chemical process, and the safe use of sodium.

A. Magnesium/Grignard Reagent Preparation and Reaction

1. Storage

NFPA 484 (8) gives the following requirements for storage of turnings or chips:

- The turnings or chips shall be stored in closed steel drums or other closed noncombustible containers, and the containers shall be stored in dry locations.
- Buildings used to store magnesium turnings or chips shall be of noncombustible, single-story construction.
- The use of automatic sprinklers in buildings storing magnesium turnings or chips shall be strictly prohibited.
- Magnesium turnings or chips shall be well separated from other combustible or reactive metals.

Grignard reagents react vigorously with water, so extreme care must be taken in drum storage and handling. Any damage to the drums could cause leakage of the contents, and if they come in contact with water, a fast, volatile reaction will occur, and rapid evolution of flammable solvent vapor can occur. A blanket of inert gas, such as dry nitrogen or argon, is required for the packaging, handling, and transport of Grignard reagents to reduce reactivity. The inert atmosphere must be maintained throughout the production and use of the reagent, both to maximize safety and to optimize yields in a Grignard reaction.

2. Handling and Reaction

When setting up a system to transfer Grignard reagent from a drum to a rector or feed vessel, the unopened drum must be properly grounded and bonded prior to the attachment of any transfer fittings, to ensure a metal-to-metal contact with the ground cable. Typically, the 2-in. drum bung is set up as the feed outlet, and the ¾-in. opening is set up as the vent. This vent is connected with low-pressure-regulated nitrogen to provide an inert atmosphere in the drum and act as a follower (purge) gas in the feed lines.

The ¾-in. venting system should include a solvent flush for rinsing residual Grignard reagent from the feed lines. This will ensure safe opening of the quick-connect junctions typically found in such systems. A pressure relief valve is also needed to prevent overpressurizing the drum. Details of such a system are shown in Figure 5.

Before disposal of the drum, it should be flushed with a gallon or two of dry solvent. The line to the receiving vessel should be flushed as well. This is followed by a flush of dry nitrogen to empty the line and purge it of oxygen. Once the pipe and fittings are removed, the drum is capped and transferred to a waste-handling pad equipped with a grounding system, water, and proper waste

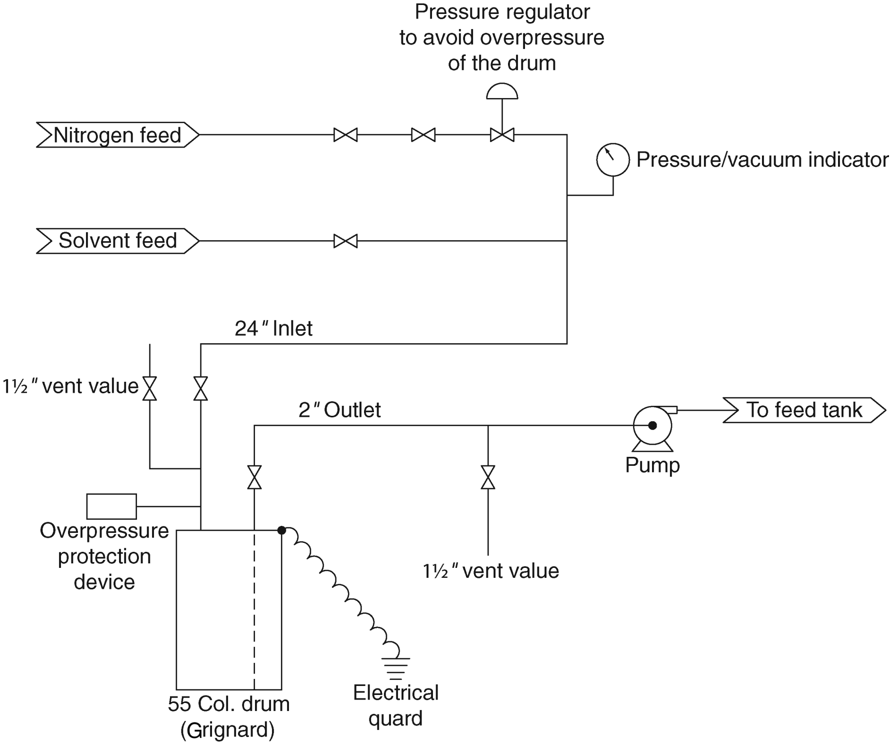
Pressure regulator to avoid overpressure of the drum
Nitrogen feed
Pressure/vacuum indicator
Solvent feed
24" Inlet
1½" vent value
2" Outlet
To feed tank
Pump
Overpressure protection device
1½" vent value
55 Col. drum (Grignard)
Electrical quard

FIGURE 5 Typical systems for transfer of Grignard drum contents.

solvent–handling facilities. The drum can now be safely filled with cold water and should be allowed to overflow for five minutes to flush away any remaining reagent or solvent. After thorough drainage of the drum, it is ready for safe disposal.

Grignard reactions are generally run using an excess of the reagent to ensure complete consumption of the organic substrate. Accordingly, when the reaction is complete, there typically remains 5% to 20% unreacted Grignard reagent in the reactor that must be disposed of properly. Both the quenching of the coupled Grignard reagent and the disposal of the unused reagent left in the drum require an additional hydrolysis step, to remove the magnesium halide.

The hydrolysis step is performed in the process vessel, which should be vented through a flame arrester. Sufficient acidified water (enough to form at least 25% $MgCl_2$ solution) is added carefully to the vessel, with good agitation and full cooling on the vessel jacket.

When performed on the reaction mass in the reactor, this hydrolysis step will create two separate, immiscible layers: the synthesized product (dissolved in ether solvent) and aqueous magnesium chloride. The heavier aqueous layer settles to the bottom of the reactor and is drained off. The desired product is then further isolated by removing the solvent. The solvent can be distilled from the product by stripping or removed by extraction. The recovered solvent is then burned in an approved facility or, if it is to be reused, is typically distilled to ensure the required purity for the next batch.

3. Hazard Control and Management

Spills. Spills of Grignard reagent should be contained with inert absorbent material, such as dry sand or earth, and transferred with nonsparking bronze, brass, or plastic tools to containers, making sure that the containers are properly grounded.

Any spilled Grignard reagent must be disposed of as a solid waste in accordance with all applicable state and federal regulations. Spilled Grignard reagents cannot be salvaged since contamination and exposure to air renders them unsuitable for use.

Fire. The hazards associated with the manufacture, transport, and use of Grignard reagents are related to the flammability of the solvents used and the exothermic reactions involved in their preparation and use.

Since the 1950s, tetrahydrofuran (THF) is the preferred solvent used in the preparation of the reagent. It is a cyclic ether, with a boiling point of 65.6°C and a flash point of -17°C.

As reactions involving the manufacture and use of Grignard reagents are exothermic, the associated heat released must be controlled. Typically, these reactions are carried out in jacketed, glass-lined reactors, equipped with cooling, explosion-proof electrical wiring and equipment, rupture disks for pressure relief, and an inert atmosphere (usually nitrogen) for purging and blanketing. When THF is used as the solvent, ambient cold water may suffice as the jacket-cooling medium. Since Grignard reagents are particularly reactive with water, organic heat transfer fluids (e.g., Dowtherm and Therminol) may be substituted for water to eliminate the risk of water leaking into the reactor from the jacket if a hole is created in the reactor inner walls.

Grignard reagents react exothermically with air, water, and CO_2. However, during a reagent fire, the major source of heat generated will be from the burning solvent. As with any solvent fire, the three primary concerns should be

1. removing the source of ignition,
2. isolating and extinguishing the fire, and
3. controlling the evolution of flammable vapors.

Because Grignard reagents are highly reactive, fires should not be put out using extinguishers containing CO_2 or chlorinated hydrocarbons, and water must not be used. Dry chemical fire extinguishers are preferred for the fighting of Grignard reagent fires. Additionally, full personal protective equipment, including self-contained breathing apparatus, is required.

Thorough discussions of Grignard reagent preparation, use, and reaction are presented by Rakita et al. (9) and Rakita (10).

B. Sodium

Sodium is used in many API processes as a reducing agent. Packaged sodium is available in drums as ingots or cast solid in drums for remelting.

1. Storage

Sodium should be stored in a dry, fireproof building in sealed metal containers under inert gas blanketing or under mineral oil. A remotely located, detached building is preferred that is isolated from other facilities or separated by noncombustible walls and seamless diked (curbed) floors. Building ventilation should be provided at the highest wall point to avoid possible hydrogen accumulation and to exhaust smoke in case of a sodium fire.

The storage space must be large enough to accommodate the maximum expected inventory of sodium and any empty containers. The building should not contain flammables, or water, and should not have a sprinkler system, water pipes, steam pipes, or skylights. Particular care must be taken to prevent water entry from roof leaks, rain, snow, or improper drainage. Potential for flooding should be evaluated. Small quantities of sodium may not need a separate building or room, but the basic requirements to prevent water contact still apply.

Drums of sodium must be stored unopened until they are ready for use.

2. Handling

When removing solid sodium ingots from steel drums, first inspect the drum to be sure that the drum is not bulged, the nut that holds the lock rim in position is unscrewed, the lock rim is removed, and the cover is pried off. Clean, dry nonsparking tools should be used. The drums are purged with inert dry nitrogen when packed, but if moisture is present during packing or from any subsequent opening, sodium will liberate hydrogen, which may form an explosive mixture with air in the confined space. For this reason, it must always be assumed that hydrogen may be present when a container is first opened. Hammering or any other activity that might cause a spark and ignite the hydrogen must be avoided. When opening a container for the first time, the cover should be lifted cautiously.

When opening or closing a sodium container, the operator should always wear protective clothing, including goggles, full-face shield, and dry hand protection, preferably moleskin mittens.

In transferring sodium from the shipping container to a distant point of use, a special metal container equipped with a tight-fitting cover should be used. Immersion in mineral oil may help in safe transfer. Because sodium picks up moisture when exposed to humid air, the container must be kept closed and preferably purged with dry nitrogen, except when sodium is being removed. For safety and convenience, iron tongs may be constructed for handling 5-lb sodium ingots (11).

Various charging gates (devices) have been designed for feeding solid sodium into reactors (11). A double gate with an intermediate chamber large enough to hold the sodium charge is used when it is important that no air be admitted to the reactor, or where burning might occur when the reactor is opened. If necessary, the intermediate chamber of the gate can be filled with an inert gas. Care must be exercised if flammable vapors are present in the reactor area, to prevent static discharge from ingots upon removal from drums and the potential for having an explosion (deflagration).

More details about handling of solid sodium, as well as liquid sodium, are presented in the DuPont manual on sodium (11).

V. CYANIDES STORAGE AND HANDLING

Several solid cyanides (e.g., NaCN, KCN, and CuCN) are used in the manufacture of APIs. For example, NaCN was used in the production of methyl dopa, and is being used in the manufacture of the anticancer drug laetrile and the blood pressure–reducing drug nitroprusside.

This section discusses practices for the safe storage and handling of NaCN, which are also applicable to other solid cyanides. Because of the toxicity of sodium cyanide, all persons working with it should be completely familiar with and observe the established safety practices.

A. Storage

Sodium cyanide is produced in briquette and granular form, and shipped in nonreturnable drums (50– and 100–kg net weight), multiwall composite bags (20 kg), nonreturnable 1000-kg (net weight) intermediate bulk containers (IBCs), and returnable FLO-BIN containers (1361– and 1497–kg net weight).

When sodium cyanide is stored, security should be maintained, so only authorized people have access to it.

Locked rooms or locked fenced areas can be used. Only the quantity required for immediate use should be removed from storage.

Drums of NaCN should be stored inside and segregated from acids, weak alkalies, and strong oxidizing materials such as nitrates. It is also recommended that NaCN be stored away from flammables and combustibles to minimize the chance of cyanide-water runoff as a result of fire fighting. Where local regulations permit, NaCN drums should not be stored under sprinklers, because it will not burn in ordinary fires, and cyanide runoff must be avoided. Storage with food or intermediates for human or animal products must be avoided.

B. Handling

If possible, open NaCN containers in the areas in which the cyanide is to be used. Remove the cover from the container, and remove the cyanide with a metal scoop or dump the cyanide from the container as required. Special adapters (a funnel with a slide valve at the discharge end) can be fitted to the open drum top so that it can be inverted and connected to a receiving nozzle on the reactor top. After the connection has been made, the slide valve can be opened and the drum contents emptied. A retractable local exhaust ventilation (LEV) hood should be located near the open drum top to control dust emissions and limit operator exposure. The exhaust air and dust should be piped to a scrubber to remove the entrained NaCN dust.

When the risk of exposure exists, such as when opening or emptying drums, operators should wear equipment for respiratory protection against toxic dust and mist; impervious skin protective clothing such as gloves (PVC or butyl rubber gauntlet type), butyl rubber Wellington boots, PVC aprons, jacket and pants or coveralls as appropriate; and chemical safety goggles (gas-tight type preferred) and/or full-face shield.

Details of unloading IBCs and FLO-BINs are presented in DuPont Manual H-37163-8 (12).

VI. HANDLING AND CONTAINMENT OF APIs

As mentioned in the section "Introduction," some APIs (also called potent compounds) are health hazardous and must be contained to prevent them from contacting operating personnel who are working with them.

Hirst et al. (13) defined five containment strategies as follows:

Strategy number	Required controls
1	Controlled general ventilation
2	Local exhaust ventilation and airflow booths
3	Barrier isolation systems whereby powder transfer within the isolator chamber itself is permitted
4	Barrier isolation systems with contained powder transfer systems or packages within them
5	Fully automated or robot-type operation. No direct operator involvement

These containment strategies are briefly discussed in the following sections.

A. Strategy 1—Controlled General Ventilation

When API solids are not health hazardous, it may be feasible to use controlled ventilation (also called dilution ventilation) in a building or room. This method controls the air environment by removing and replacing contaminated air before concentrations reach unacceptable levels. In general, dilution ventilation is inappropriate for API solids of high toxicity where the concentrations fluctuate or where the operator works close to a point of release of contaminant.

The location of the exhaust fan and air inlet requires careful consideration in order to provide a suitable airflow pattern in the room to ensure operator exposure is minimized. Detailed information on the design of controlled (dilution) ventilation systems can be found in the books by the American Conference of Governmental Industrial Hygienists (ACGIH) (14) and Burton (15).

B. Strategy 2—Local Exhaust Ventilation and Airflow Booths

LEV removes contaminants (API solids) from the source (equipment) directly into a ventilation system; that is, the arrangement of exhaust equipment is such as to envelop the source of contaminants before they can escape into the environment. It does not rely on the dilution or displacement effects of general ventilation. It should be designed to remove the contaminant from around the source rather from around the operator.

An LEV system usually consists of the following elements: (*i*) contaminant source, (*ii*) capture hood (booth), (*iii*) ducting, (*iv*) contaminant collection/ removal equipment, and (*v*) exhaust fan.

1. Contaminant Source

The contaminant source is the process equipment from which the API dust is emitted. The main problem with designing an effective LEV system is the dispersion of dust from the source. Once it has escaped from the immediate area of the source, it is very difficult to bring it under control. It is necessary, therefore, to obtain information on the behavior of the dust leaving the source, such as its direction and velocity. The air currents, which influence the behavior of the dust, should also be studied.

2. Capture Hood (Booth)

There are two basic types of capture hood or booth systems in a LEV system: (*i*) enclosures and receptor hoods and (*ii*) captor hoods. Enclosures may be either total or partial. With a receptor (capture) hood, the emission source is either inside or at the mouth of the hood. The hood receives dust-laden air brought into it by air currents. These are either hot air currents rising from the process or cold air currents induced by the process. Total enclosure is the most effective arrangement, but is not always practical. Where a total enclosure is used, it needs to be airtight so that it contains the dust handled, and strong enough to remain so. If a partial enclosure is used, it should be no larger than necessary for the purpose. The velocity of the air entering it should be high enough to overcome any tendency for the air inside to escape.

The other main type of hood used in LEV systems is the captor hood. Whereas a receptor hood receives a flow of dust-laden air carried into it, a captor hood draws the airflow in. The two types of hood may sometimes be similar in shape, but the principle of operation is different. A receptor hood operates on the "push" principle, while the captor hood operates on the "pull" principle. For a captor hood, the air velocity required depends critically on the distance between hood face and the contaminant source. The performance of a captor hood may be enhanced by the use of flanges around the face inlet. The flanges eliminate airflow from ineffective zones where no contaminant exists.

Discussions of LEV systems and their design are presented in books by the ACGIH (14) and Burton (15).

3. Ducting

When handling combustible API dusts, ducting should be fabricated of metal or other noncombustible material, and should be of adequate strength and rigidity to meet service (temperature and pressure) conditions and installation requirements. Where exterior insulation is used on duct systems, it should be noncombustible.

Ducts of plastic material and plastic-lined metal ducts should be used only for noncombustible dusts. If they pass through an area where combustible materials are stored or processed and a fire could occur, these ducts should be protected by a sprinkler system.

Ducts conveying API solids should be designed for a gas (air or inert gas) velocity high enough to prevent particles from settling out and depositing inside of the duct. Accumulation of combustible dust inside of ducts can lead to fires and explosions, and possible system shutdown if the accumulation becomes too great. Also, the conveying ducts may not be strong enough (they are often made of thin-wall sheet metal) to contain heavy solids accumulation and may collapse, emitting API solids into the adjacent areas. This should be considered, and if necessary, adequate supports should be provided under the duct. The ACGIH book (14) gives recommended velocities for conveying of dusts and powders in ducts to prevent or minimize settling out of dust.

4. Contaminant Collection/Removal Equipment

The API dust from the LEV system ducting should be directed to dust collection equipment, such as dry collectors (baghouse or cartridge types), or to wet scrubbers. Descriptions and discussions of these types of scrubbers are given in Perry's handbook (16) and Croom's book (17).

If the dusts are combustible, the scrubbers should be equipped with deflagration vents, designed in accordance with procedures given in NFPA 68 (18).

C. Strategies 3 and 4—Barrier Isolation Systems

The differences between containment strategies 3 and 4 have been brought about by the realization that the weak links in any barrier isolation system are the inlet and outlet transfer doors/valves/ports. These could be double transfer ports, split butterfly valves, or the like. When these ports are contaminated with toxic solids, it is inevitable that some emission of material will occur due to either poor maintenance or ingress of the powdered material itself into the finely machined faces of these transfer ports. As such, this may bring about a risk of solids emission. Containment strategy 4 eliminates this risk by requiring that all powder transfers within the isolator body are fully contained. Here, the isolator provides an outer layer of containment and an extra level of safety for the operators.

Barrier/isolator systems are made up of four basic parts: the physical structure, the internal environment, the transfer and interaction technologies, and the monitoring systems. Within each of these parts, there are a series of choices that will greatly impact the success of the containment.

The physical structure of a barrier/isolator is generally classified by the appearance of the structure and falls into two categories: hard shell and soft shell. The next level of differentiation is the materials of construction, with the choices for the hard shell being plastic, plexiglass, glass, and/or stainless steel and the choices for the soft shell being a soft plastic or otherwise flexible film. Important issues concerning the construction of the shell are mainly the following three: durability or integrity of the system, ability (or need) to have cleanable surfaces, and visibility of internal operations.

The durability of the barrier/isolator should be consistent with the environment in which the unit will be used, the process and tools involved, and the frequency of use.

The cleanability issue involves the quality of finish, welds, joints, and corners. A number 4 finish is often used. The issue of welds and joints is important. Joints around penetrations such as viewing areas, air inlets and exhausts, and other required components should be smooth and free of ledges. Materials used for gaskets need to be checked for durability and compatibility with the powders handled. Effects of exposure to cleaning agents should also be checked.

Visibility is also an important consideration in API production and handling, as they require a number of interactive steps, including visible checks of activities.

The internal environment of a barrier/isolator is usually negative pressure, and is a form of secondary containment to the system and should be designed to allow for protection from a breach of the barrier. The most common breach is a glove port or bag ring not properly sealed or torn during operation. The internal airflow of a barrier/isolator designed for containment should allow clear viewing of the operation and removal of any heat generated by the process equipment contained in the system. Lighting should be located exterior to the barrier/isolator structure with see-through panels allowing the light to enter. Utilities can be provided interior to the barrier/isolator through several means, including fixed panels inside or flexible connection ports. Attention must be paid to potential electrical hazards that could be present from solvents or dust.

Transfer of materials between a barrier/isolator and the outside, without exposure of the operator to the potent compound, is one of the biggest challenges of any system. The transfer can be accomplished by the following technologies: double-posting port, bag rings, air lock, and airflow.

The double-posting port is the mainstay of high-integrity transfer technology. It is also called a rapid transfer port (RTP). The double-posting port design and several variations are manufactured by a number of vendors. The basis of this component is a double door, capable of separating to form two seals for separate enclosures, allowing both to maintain integrity. These ports enable hazardous materials to be transferred from a container into an isolator and vice versa without loss of containment. Both the container carrying the hazardous material and the wall of the isolator must have compatible port designs: the alpha assembly, built into the wall of the isolator, and the matching beta assembly, which closes off the container. Both assemblies comprise a frame holding a circular door, which cannot be opened unless a matching assembly is docked in place, in which case the two doors open together as one.

The split butterfly valve technology permits the docking of a precharged container onto a process vessel without the need for a second isolator glove box required for the RTP. The valve provides a way to transfer particulate solids between vessels with a high level of containment, allowing solids to flow out of the bottom opening of one container fitted with one-half of the valve into the top opening of another container equipped with the other half of the valve. The split butterfly valve, as its name implies, is effectively a single butterfly valve that is split into two parts, generally along the long dimension of the disk to make two flappers. One matching part (called the passive valve) closes off and seals the bottom of the upper container holding the powder, while a matching half (called the active valve) seals the inlet connection of the lower receiving vessel. Split butterfly valves must always be closed when the two parts are separated. Only when both valve halves are docked together, using a centering and locking pin that is vertically positioned, to form a complete connection, do interlocks release to permit the combined disk to rotate 90° to open and permit transfer of the powder from the upper to the lower vessel. After transfer is completed, the valve halves (combined disk halves) are rotated back to the closed position, and inflatable seals about the vertical pin on the passive side of the valve and about the circumference of the active part of the valve are inflated to seal. The two containers are then separated by separating the valve into the original two halves that are connected, respectively, to the bottom of the upper vessel and the top of the bottom vessel.

Bag rings involve the use of plastic sleeves or bags to introduce solid materials into or out of a barrier/isolator. The method is more procedure dependent in sealing technique, but has proven effective in handling potent compounds. Bag rings come in a variety of sizes and shapes to meet requirements and offer flexible means of transfer.

Monitoring of operations is critical for providing a safe workplace. Developing a plan or strategy for measurement of the levels of potent compounds outside of the containment system is necessary. The measurement program should involve both facility and personnel monitoring. Barrier/isolator monitoring can be done by any of the three following methods: pressure detection, air filter leak detection, and gas leak detection.

Pressure detection is used to determine pressure difference. Devices may be simple as gauges, with visual readouts, or units connected to alarms.

Online feedback is important when dealing with very potent compounds, and this can be provided by air filter leak detection. The pressure drop approach to monitoring filters is not sensitive enough to detect a leak of quantities that are above exposure levels. Online particle counters are recommended after the filtration system to determine integrity of filters for compounds having an exposure limit below $10\,\mu g/m^3$. These systems can be integrated with facility information systems for record keeping and alarming.

Gas leak detectors, such as oxygen analyzers, can be used to determine proper processing environments and to act as a personnel alarming device. Gases such as helium can be used internally to the barrier/isolator for detection of extremely potent compounds. Integration with information systems for record keeping should be considered.

D. Strategy 5—Fully Automated or Robot-Type Operation

This strategy is adopted for APIs so hazardous that even with a closed transfer system the use of a glove-port represents an unacceptable risk because of the possibility that the gloves could tear or repture. The transfer therefore has to be affected by a fully automated closed operation where all operator input to the process will be via remote control.

Some general design practices for a typical facility handling toxic powders (loading dissolvers and/or reactors, unloading centrifuges, loading and unloading dryers, and powder formulation equipment) are presented by Dream (19).

Two comprehensive sources of information on API containment are the books by Hirst et al. (13) and Wood (20).

Clean rooms are frequently used in the final finishing steps of the manufacture of pharmaceuticals from APIs to prevent contamination of the product. They are classified by the cleanliness of their air as given in ISO 14664-1 (21).

Clean rooms can be divided into four main types as follows:

1. Conventional: these clean rooms are also known as turbulently ventilated or nondirectional flow and are distinguished by their method of air supply, that is, the air is supplied by air supply diffusers in the ceiling.
2. Unidirectional flow: this was previously known as laminar flow. Clean air is supplied from a bank of high-efficiency filters and passes in a unidirectional manner through the room.
3. Mixed flow: this type of clean room is conventionally ventilated, but where the product is exposed to contamination, a unidirectional flow cabinet or workstation is used.
4. Isolators or microenvironments: these are used within a clean room to give the highest level of protection against contamination. The isolator has a unidirectional supply of air, but this may be a conventional turbulent flow type.

Grossel and Zalosh (22) present an overview of clean room design and operation.

VII. REACTOR DESIGN AND OPERATION

A. Introduction

APIs usually are produced in vertical, agitated, jacketed reactors, operating in the batch or semi-batch mode. A number of hazards can occur during reactor operation, and this section discusses these hazards and practices that can be used to minimize or eliminate them.

The following topics are discussed in this section:

- Reactor mechanical design (design pressure)
- Charging of liquid reactants/solids into reactors
- Purging and blanketing
- Agitation
- Runaway reaction causes and methods to minimize them
- Overpressure relief
- Heating and cooling systems
- Precautions for glass-lined reactors

B. Reactor Mechanical Design (Design Pressure)

For reactors fabricated of metal only (not glass lined), it is recommended that a minimum design pressure of 50 psig be specified, even if the operating pressure is essentially atmospheric. This provides inherent safety for unexpected pressure swing events (pressure spikes). If an explosive mixture might occur that could result in a deflagration, then tests should be performed to ascertain what the maximum pressure would be, and the design pressure specified accordingly, taking into account whether it is acceptable for the vessel to be deformed ("bulged") or whether no deformation is acceptable (23).

C. Charging of Liquid Reactants/Solids into Reactors

All flammable liquid reactants should be charged into a reactor via dip legs or elbows pointed toward the wall, which will cause the liquid to run down the reactor wall to avoid static electricity generation.

Where solids have to be added to a reactor containing flammable or toxic liquids, they should be charged via a closed charging system, and not through an open manhole. In past years, charging of solids through an open manhole into a reactor containing flammable liquids has resulted in flash fires and deflagrations that caused bodily harm or death to the operators. There are a number of closed charging systems that can be used, such as the following:

- Charge hopper or drum dump station with a rotary discharge valve (Fig. 6).
- Charge hopper with a "double dump" discharge valve (Fig. 7). This is commercially available from a number of solids-handling valve manufacturers.
- Charge hopper with a screw or vibrating conveyor connected to a nozzle on the reactor head.
- Vacuum pneumatic conveyor/filter receiver system to convey solids from a drum to the reactor.
- Powder transfer system. This is a proprietary system similar to a vacuum transfer system.

D. Purging and Blanketing

When a reactor is to be charged with a flammable liquid and/or combustible solid, it should first be purged with an inert gas (usually nitrogen) to reduce the oxygen concentration in the reactor to be below the limiting oxidant concentration (LOC) and prevent the potential for a fire or deflagration. There are four

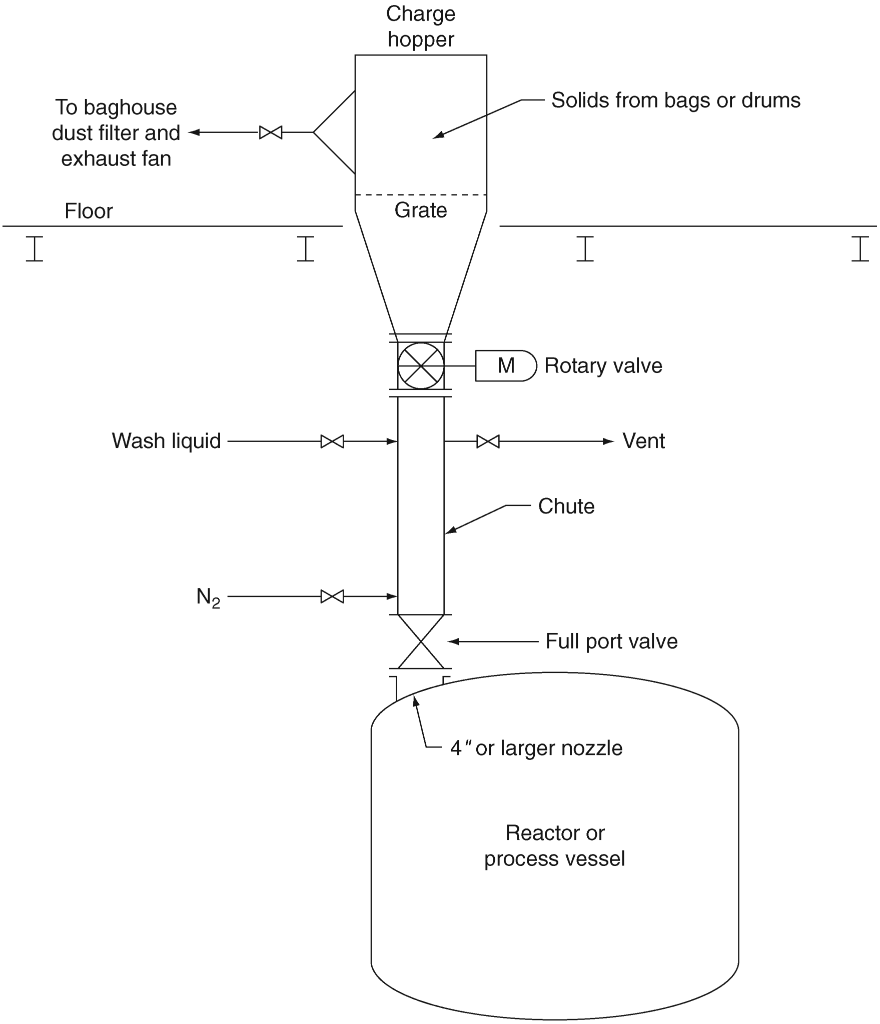
Charge hopper
To baghouse dust filter and exhaust fan
Solids from bags or drums
Floor
Grate
M
Rotary valve
Wash liquid
Vent
Chute
N_2
Full port valve
4″ or larger nozzle
Reactor or process vessel

FIGURE 6 Charge hopper with rotary discharge valve.

ways to purge a reactor: (*i*) pressure purging, (*ii*) vacuum purging, (*iii*) combined pressure-vacuum purging, and (*iv*) sweep-through purging. These are discussed in NFPA 69 (23) and Crowl and Louvar (24), which present equations for calculating the required amount of nitrogen to reach the desired LOC. Sweep-through purging should always be done by introducing the nitrogen into the bottom of the reactor so that it flows upward throughout the entire reactor volume. Introduction of the nitrogen through a nozzle on the reactor head may cause the nitrogen to become "short-circuited" and flow out through the vent nozzle so that the entire reactor volume is not purged.

Blanketing, also called padding, is used once the reactor begins operating to prevent the ingress of air. Besides lowering the LOC to a safe level, blanketing

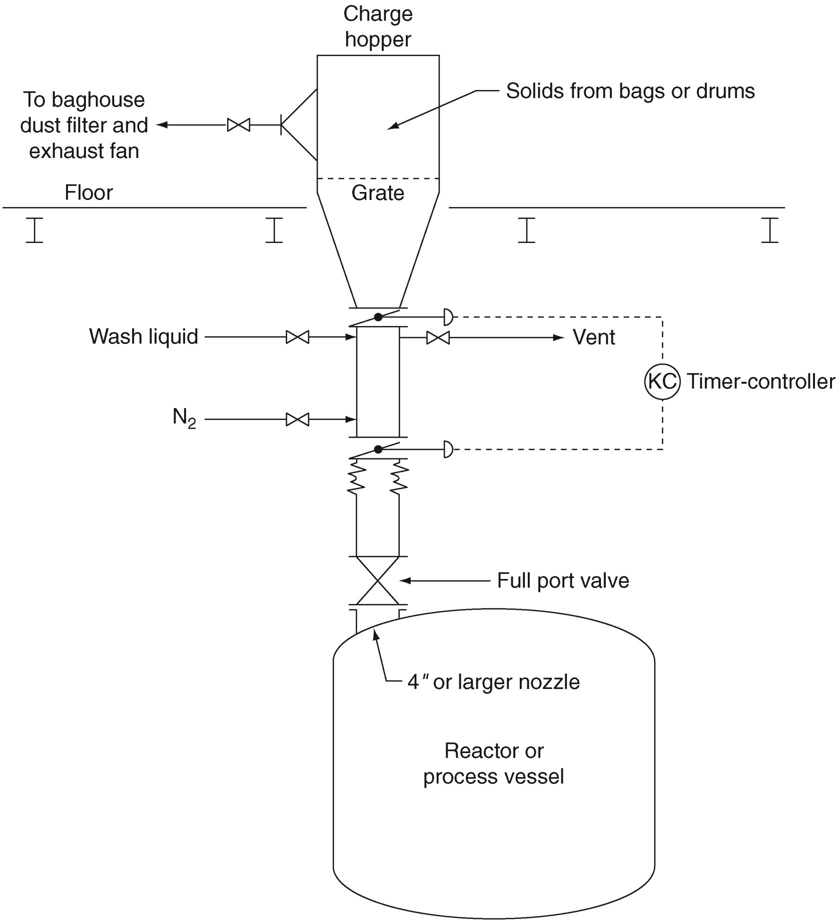
Charge hopper
To baghouse dust filter and exhaust fan
Solids from bags or drums
Floor
Grate
Wash liquid
Vent
KC Timer-controller
N_2
Full port valve
4″ or larger nozzle
Reactor or process vessel

FIGURE 7 Charge hopper with "double dump" discharge valve.

is also sometimes required where the reactants, products, or solvents are subject to peroxide formation or oxidation to form active compounds (e.g., acetylides) or where they may be degraded by atmospheric oxygen.

Where it is critical to have continuous blanketing, it is imperative that an inert gas supply of sufficient capacity be ensured and the supply pressure be monitored continuously. Consideration should be given to providing a "backup" source of nitrogen if the plant nitrogen system is disrupted. This can be provided by connecting a bank of nitrogen cylinders to the main supply header, which will be activated if the main nitrogen supply header pressure drops to a low value.

A check valve or other suitable device should be provided at the inlet to a reactor in the branch line from a nitrogen header. This will prevent contamination of the nitrogen system through a drop in nitrogen pressure or excessive pressure in the reactor. An additional check valve or other suitable device should be provided on the discharge side of the supply header.

The nitrogen system piping should be electrically grounded and bonded to minimize static electricity.

E. Agitation

Good agitation is necessary to efficiently mix reactants, solvents, and catalysts. Agitation equipment should be specified and designed for reliable service with consideration of the following factors:

- Design the agitator to withstand maximum process temperatures and pressures.
- Design the agitator to function under all foreseeable viscosity conditions.
- Use a variable speed design agitator with limited shaft speed. Monitor shaft speed and load.
- Provide adequate cooling for shaft seals and bearings. Hot bearings and seals are potential ignition sources. Provide vibration or temperature sensors here if this is a concern.
- Use double or tandem mechanical seals with inert seal fluid when seal failure could release flammable or other hazardous materials, especially hydrogen. Provide low-level alarms on seal fluid reservoirs.

F. Runaway Reaction Causes and Methods to Minimize Them

Runaway reactions may be caused by the following conditions:

- Too-fast addition rate of a reactant or catalyst
- Overcharging of a reactant or catalyst
- Loss of agitation
- Inadequate and/or loss of cooling

These causes and methods to minimize them are discussed below:

1. Too Fast Addition Rate of a Reactant or Catalyst

This can be avoided by installing a restriction orifice in the feed line to the reactor from a head tank or from a feed pump. In addition, a high-temperature sensor in the reactor can be interlocked with an open-shut valve in the feed line to stop the flow of reactant or catalyst.

2. Overcharging of a Reactant or Catalyst

Where overcharging (adding too great an amount) of a reactant or catalyst can cause a runaway reaction, the use of a gravity flow head tank, sized to hold only the quantity needed, will prevent this from happening.

3. Loss of Agitation

A runway reaction can be caused by the following two loss-of-agitation conditions: (*i*) loss of electricity to the agitator motor due to a plant power outage and (*ii*) unrecognized cessation of agitation due to the impeller having fallen off the shaft or being corroded out.

To protect against a power outage, a backup power supply such as an uninterrupted power supply (UPS) should be provided for critical reactions.

To protect against an unrecognized cessation of agitation, a malfunction detector can be installed in the reactor in the vicinity of the impeller (an ammeter is not adequate to detect agitation stoppage). The detector should have an alarm and be interlocked to cut off feed of reactants or catalysts and to ensure an appropriate restart sequence. Details of such a detector used successfully in industry are given by Wilmot and Leong (25).

4. *Inadequate and/or Loss of Cooling*

A runaway reaction can occur due to inadequate and/or loss of cooling water supply to the reactor jacket due to a failure of the plant cooling water supply system. An emergency cooling water supply can be provided by tieing in the plant cooling water system with the firewater system, which is normally provided with firewater pumps driven by diesel or gasoline engines as well as electric motors.

G. Process Measures for Preventing Runaway Reactions

Where runaway reactions are known to occur, and an excessively large relief device is needed, consideration should also be given to providing means to inhibit (kill or "short stop") the reaction or drown (quench) the batch. It is recommended that independent and redundant temperature instruments in the reactor be interlocked to actuate any of the following remedial actions at a specified high-temperature reading:

- Add a considerable amount of coolant or diluent to reduce the reaction rate. This measure requires that process design and detailed design provide for the following: (*i*) an appropriate fluid that does not react too exothermically with the reaction mixture is chosen, (*ii*) there is sufficient free volume in the reactor to accommodate this extra liquid, and (3) piping and instrumentation are installed to add the fluid in the time required.
- Rapidly depressure the reactor if it is under pressure.
- Add an inhibitor to stop the reaction. This measure requires intimate knowledge of how the reaction rate can be influenced and whether effective mixing/inhibition is possible. Agitation is a critical factor, especially to ensure that a small amount of an inhibitor must be dispersed homogeneously in a large volume of reaction mixture.
- Dump the reactor contents into a vessel that contains cold diluent. This option also requires particular care that the dumping line is not blocked or does not become blocked during the dumping procedure.

H. Overpressure Relief

Overpressure in a reactor is caused primarily by heat absorption from an external fire or by a "runaway" reaction.

The design of jacketed reactor relief systems for exposure to external fire is discussed by Hauser et al (26).

The design of relief systems for runaway reactions is different than for non-runaway conditions. Experimental data for the rate of temperature rise with time (dT/dt) and the rate of pressure rise with time (dP/dt) are needed for vent-sizing calculations. These are determined using specialized adiabatic calorimeters, as described in the CCPS Guidelines book (27). The design equations used for sizing depend on whether the runaway reaction is one of the following: (a) tempered, (b) gassy, or (c) hybrid. These reactions and calculation procedures for emergency relief device sizing are also discussed in the CCPS Guidelines book (27).

I. Heating and Cooling Systems

Heat removal systems for reactors should be designed with abnormal operating conditions taken into account. For reactions where a runaway can occur, the heat removal system should be capable of functioning at the temperatures achieved during the runaway reaction, although it may not have the capacity to stop the runaway. In previous years it was common practice to heat with steam and cool with calcium chloride brine in the jacket. This often resulted in stress corrosion cracking and subsequent vessel and/or jacket failure. This practice should be avoided.

Where heating and low-temperature cooling are required, a heat transfer fluid cooling/heating package should be provided. Depending on the heat transfer fluid selected, appropriate safety and occupational health practices should be followed. Information on this can be found in a CCPS Guidelines book (28).

J. Precautions for Glass-Lined Reactors

Glass-lined reactors are used extensively in the production of APIs. They can be used reliably to contain corrosive, flammable, and toxic chemicals, if they are specified, installed, and operated correctly. However, their use for alkaline solutions (up to a pH of 14) should be limited to temperatures of 50°C.

Erosion, corrosion, and mechanical, thermal, and operating abuses, however, can lead to major failures. The problems of thermal shock and corrosion are discussed in the following sections.

1. Thermal Shock

Heating and cooling cycles in a glass-lined reactor can cause thermal shock damage if proper consideration is not given to the batch liquid and heat transfer fluid temperatures. Thermal shock failure occurs due to abrupt changes in temperatures of the glass lining and results in relatively small, but thick, pieces of glass spalling off in rigid fractures. Depending on the contour of the area and the manner in which thermal shock occurs, the failure may exhibit a shattered or "elephant skin" appearance. In most cases of thermal shock, the steel substrate will be exposed.

There are four operations in which sudden temperature variations can cause thermal shock:

- Sudden cooling of a glassed surface by subjecting a preheated surface to a cold liquid
- Sudden heating of the vessel wall by rapid circulation of a very hot fluid through the jacket of a cold vessel
- Sudden heating of the glassed surface by introducing a hot liquid into a cold vessel
- Sudden cooling of the vessel wall by rapid circulation of a cold fluid through the jacket of a preheated vessel

In the first two operations, the glass lining tends to lose compressive stress, causing the lining to weaken. In the second two operations, the glass lining is subjected to sudden overcompression, causing the glass to fail. Reactor manufacturers can provide limits for the rate of temperature change for glass-lined reactors.

2. Corrosion

When specifying a glass-lined reactor, careful thought must be given to what chemicals are in the reactor and what the temperatures are during the batch cycle. It must be understood that glass is not completely inert and is always undergoing local chemical reactions at its surface. What allows glass-lined steel to be used with corrosive chemicals is the low rate of reaction (kinetics): the slower the rate, obviously, the longer the glass will last.

Acids, alkalis, and even water can corrode glass in varying forms and degrees. Strange as it seems, ultrapure water can cause severe corrosion. The corrosion rate also increases with increasing temperature and becomes greatest when the boiling point is exceeded. A small amount of acid added to water will greatly retard corrosion caused by water vapor condensation in the vapor space. This type of corrosion can also be reduced or eliminated by the introduction of an inert gas insulating the vapor area. These are important factors to consider in steam distillation processes carried out in the reactor.

Glass-lined reactors should be periodically inspected for the presence of pinholes. Pinholes are often caused by electrostatic discharges that occur when filling a reactor with a flammable liquid. Pinhole leaks can rapidly develop into a major problem. Pinholes can be identified by spark tests or by using a continuous electrical surveillance technique.

Grossel and Crowl discuss other precautions for glass-lined reactors (29). Additional information on batch reaction systems safety is presented in a CCPS book on this subject (30).

VIII. PRESURE RELIEF AND EFFLUENT HANDLING

A. Pressure Relief

Besides providing pressure relief for reactors, safety relief valves or rupture disks have to be provided for the protection of other items of process equipment used in the manufacture of APIs, for example, process vessels, heat exchangers, pressure filters, and pumps.

Some common causes of overpressure in process equipment are as follows:

- Exposure of process vessels to an external fire
- Exposure of storage vessels and pipelines to strong sunlight
- Equipment failure (such as pumps and heat exchanger tube failure)
- Reflux failure on a distillation column
- Excessive operating heat input or high pressure as a result of some control failure
- Failure of cooling water to a heat exchanger
- Valve failure (e.g., locking in the open or closed position)
- Blocked outlets (e.g., inadvertent valve closure on process equipment)
- Line blockage/plugging
- Mixing of hot and cold streams (water with hot liquid or a cold organic into a hot liquid)
- Operator error

These causes (and others) are discussed in API RP 521 (31) and the CCPS Guidelines book on pressure relief (27). Procedures are also given in them for calculating the resulting flow rates that need to be used for sizing a relief valve or rupture disk.

The relief device should be installed as close as possible to the protected vessel (preferably on the top head) or other equipment so that the device will be properly fed with relief effluent under flowing conditions.

The discharge piping on the outlet of a relief device should be as short as possible. Changes in direction and elbows should be kept to a minimum.

B. Effluent Handling

When the contents of a vessel or other item of equipment cannot be safely discharged to the atmosphere (e.g., they are highly flammable, toxic, or corrosive), they should be routed to containment and/or control equipment such as a catch tank, knockout drum, quench tank, emergency scrubber, or flare system. Effluent handling procedures and equipment are discussed and described in detail in a CCPS Guidelines book on this subject (27).

IX. FIRE AND EXPLOSION PROTECTION

Most API manufacturing is done in buildings, and the building and equipment must be protected from fire and explosions. These are briefly discussed in the following.

A. Fire Protection

All process equipment containing flammable liquids should be protected against fire by the installation of fixed water spray systems. Water spray nozzles are of two types: (*i*) closed head and (*ii*) open head (deluge). Deluge systems are used for special hazards where rapid fire spread is a concern, and many API manufacturing plants use them, especially for reactor protection. The deluge nozzles are located above the reactor and below the reactor bottom head (the reactor is elevated by pipe or angle iron support legs or hung between beams).

Water spray nozzles should be placed to provide direct impingement of water on processing equipment and supporting structures.

Fixed water spray systems should be designed and installed in accordance with NFPA 15 (32). Another useful source of information on fire protection is the CCPS book on this subject (33).

B. Explosion Protection

Explosion protection is actually somewhat of a misnomer, as it actually means protection of buildings and equipment against the effects of a deflagration. A deflagration is defined as propagation of a combustion wave (flame front) through a fuel-oxidizer mixture at a rate that is less than the speed of sound in the unreacted medium and capable of producing a significant increase in pressure. This section briefly discusses methods to protect buildings and equipment against pressure increase due to a deflagration.

1. Buildings

If there is a possibility of a deflagration occurring in a building (or rooms in a building) due to emission of a flammable gas/vapor or combustible dust, deflagration protection should be provided. This can be done by deflagration venting or deflagration suppression. If the gas/vapor or dust is not toxic or health hazardous, then venting is a feasible choice, provided that there is enough wall and/or roof area for the vent area needed. The vent area calculated is usually provided by installing "blowout panels" in an outside wall so that the pressure produced by the deflagration is vented to the atmosphere. NFPA 68 (18) presents a method for calculating the required vent area for a building (or room) in its section on low-strength enclosures.

If the gas/vapor or dust is toxic or health hazardous, then deflagration suppression should be used. In previous years Halon 1301 was commonly used for deflagration suppression, but it is no longer being used as it is harmful to the ozone layer. Some substitutes now in use are HFC-227ea (sold as FM-200 or FE-227) or HFC-236fa (sold as FE-36). Other suppressants such as water and dry powders (alkali metal bicarbonates, ammonium phosphates, and substituted ureas) are also used.

Information on deflagration suppression is presented in NFPA 69 (23) and by Grossel and Zalosh (22).

2. Process Equipment

Protection of process equipment against a deflagration can be accomplished by the following methods:

- Deflagration venting
- Deflagration suppression
- Deflagration pressure containment
- Deflagration isolation systems

Deflagration venting. As with buildings, deflagration venting may not be acceptable for vapors/gases and dusts that are toxic or health hazardous unless they can be directed to containment or control equipment that will not allow them to come in contact with operators. If the deflagration products are not toxic or health hazardous, then conventional venting may be feasible. Methods for calculating vent areas for gas/vapor and/or dust deflagrations are given in NFPA 68 (18) in its section on high-strength enclosures. If the process equipment is located inside of a building, then the deflagration combustion products have to be vented to the outside of the building to a safe location. This requires that a vent duct be attached to the vent closure to direct the combustion products to the outside. The addition of the vent duct results in a larger vent area needed than without the duct. Alternatively, a flameless vent device (combination flame arrester and particle filter) can be attached to the vent closure, so that a vent duct is not required.

NFPA 68 also discusses many other topics about venting systems, such as types of vent closures, fireballs and external pressure effects, and reaction (recoil) forces.

Deflagration suppression. Deflagration suppression is also a very widely used protective measure in chemical processing industries. It is often used where it is not possible to vent the contents of process equipment and vessels to a safe place.

The system consists of a sensor(s), control package, and suppressant bottle (s) containing a suppressant. This method requires that an incipient deflagration be detected very soon after ignition, and that a sufficient amount of suppressant is discharged into the growing fireball in the enclosure at a fast enough rate to extinguish all flame before a destructive overpressure develops.

NFPA 69 (23) discusses the various components of a deflagration suppression system, as does Grossel and Zalosh (22), in more detail.

Deflagration pressure containment. Deflagration pressure containment is a technique for specifying the design pressure of an item of process equipment and appurtenances so that they are capable of withstanding the maximum pressure resulting from an internal deflagration.

Containment for process equipment can be specified as either explosion pressure–resistant or explosion pressure shock–resistant. Explosion pressure–resistant equipment should not be ruptured or deformed in any way in the event of a deflagration. Explosion pressure shock–resistant equipment can be expected to deform, but not rupture in the event of a deflagration.

NFPA 69 (23) presents equations for calculating the design pressure required for both types of containment and also discusses other aspects of this protection technique.

Deflagration isolation systems. Items of equipment in process plants are often connected by piping, ducts, chutes, and conveyors. A deflagration that is initiated in one equipment item can propagate along these interconnecting links and start a subsequent deflagration in other equipment both upstream and downstream. Isolation methods can be used to interrupt or mitigate flame propagation, deflagration pressures, pressure piling, and flame-jet ignition between items of equipment.

The following types of isolation methods (devices) can be used: (*i*) automatic fast-acting valves, (*ii*) flame front diverters, (*iii*) flame front extinguishing systems (chemical suppressant barriers), and (*iv*) material chokes.

NFPA 69 (23) discusses these four types of isolation devices, as does Grossel and Zalosh, in more detail (22).

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12 Plant Operations

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I. PLANT ORGANIZATION

The first step is the planning of the organization of the plant. I will, in this discussion, make certain assumptions about the company. In any large company many of the necessary activities required for an active pharmaceutical ingredient (API) business operation, other than the pure production operations themselves, would usually be the responsibility of separate organizations within the company.

There are usually four specific organizational areas required in any manufacturing plant organization. These are the manufacturing operations themselves, plant maintenance, materials management, and quality control and assurance. The last three activities are the subject of individual chapters in this book, and I refer the reader to those. I will concentrate on the manufacturing operations and restrict my comments on other subjects covered separately in other chapters to broad generalities. The full chapters should cover the appropriate details.

Other key activities pertinent to API manufacturing are also the subject of separate chapters in this volume. These include process development, plant design, and regulatory activities that are all critical to the initiation and approval of any plant. However, these activities, in any large organization, are separate functions that interact with the plant. Process development, as well as regulatory operations, is traditionally part of a corporate research division, while plant design would generally be part of a corporate engineering function. In addition, the subjects of safety and environmental control are very significant to an API manufacturing facility and are handled as separate chapters in this volume.

The interaction of the plant with the research and development area will be most significant during the design and start-up phase of the plant and each of its products. The regulatory activities that would be required for the preparation and filing of the required documentation for the Food and Drug Administration (FDA), in the United States, or the health ministry of the country where sales are planned. These will be the subjects of discussion in the appropriate chapter.

II. BATCH VERSUS CONTINUOUS OPERATIONS

The evolution of the industry has seen an interesting shift. The early days of API manufacturing, particularly in Europe, were focused on the input of "industrial chemists" who developed the complex multistep processes often required to achieve the unique structure of the product. This, in combination with the relatively small commercial requirements, led to relatively small-scale batch operations with batch equipment in the 100–500-gal size. Generally the equipment was a relatively small scale-up from the laboratory and mirrored the laboratory operation. This was more than adequate to meet the then small market needs. In addition, new product production requiring different equipment needs would be met by building another small factory within the plant and resulted in a plant maintaining many small dedicated operating factories.

As the business of pharmaceuticals rapidly grew, particularly in the 1940s and 1950s, the kilogram requirements for most specific APIs leaped. This drove the need for larger vessel volume and more complex batch systems. This in turn drove the capital cost up at a time when equipment costs were already rising.

Furthermore, during these decades other impacts began to weigh on the capital and operating costs of each and every factory in a plant. These were the new issues of environmental impact and control and the increased safety and personnel exposure control mandated for each operating unit. All of these factors increased the cost to operate each separate unit. This gave impetus to allow the growth of the input of the chemical engineer rather than the chemist on the transfer of the process from the laboratory to the commercial scale. In these years, particularly in the United States, the application of more traditional large-scale continuous manufacturing techniques already in use in the high-volume petrochemical and heavy organic chemical industry was introduced. This became possible only because the much larger requirements for the API from thousands to millions of kilograms per annum because of the rapidly expanding market. In addition, continuous processing was often superior to batch processing because of the increased efficiencies that were possible and, very significantly, the ability to limit time and temperature conditions to the more-temperature-sensitive molecules now often being demanded for the newer products.

Surprisingly the increased material requirements, driven by explosive product volume growth, have seen a compensating effect in recent years. Although the growth of market volume continues to increase requirements for product, the new research techniques developed in the 1980s and 1990s have resulted in much more potent products, greatly reducing the quantities of APIs needed for the market. As an example, the first truly antihypertensive drug, methyldopa, initially marketed in the 1960s, had a 250- to 500-mg dose regimen. Hence, for each billion tablets required for the market (the quantities that tablet requirements had become) about 400,000 kg of drug was needed. Today, the most popular medications to control blood pressure are angiotensin-converting enzyme (ACE) inhibitors, which require only a 5-, 10-, or 20-mg dose regimen. Thus for that same one billion tablets, only about 10,000 kg of bulk drug is needed for 10 mg tablets. The net result of this was a refocus on batch operations for most APIs.

III. DEDICATED VERSUS SHARED MANUFACTURING FACILITIES

A number of factors have led to the shift from dedicated to shared manufacturing facilities for APIs. The first is, again, the increased potency of APIs and hence the reduced quantities required to satisfy the market requirements.

The second is the increasing capital cost requirements for a facility. This cost increase starts with normal inflation trends over the years and has added to it a number of other factors. One being the increased sophistication of the chemistry that is required by the increasingly complex chemical moieties being synthesized on a commercial scale. Today, what had been strictly laboratory procedures and unit operations, such as chromatography, have become routine plant operations. In addition to these more nontraditional operations on a commercial scale are the sharply increased regulatory requirements introduced in the 1970s as current Good Manufacturing Practices (cGMPs). One then adds as well to the operational issues those of waste management, environmental concerns, and safety and employee exposure.

The final point is the normal economics of larger-scale production. If one continued to utilize dedicated facilities for each product and was even willing to spend the capital needed, he or she would be faced with the higher unit operating costs associated with smaller batch sizes required to operate for each API that resulted from the reduced requirements of APIs. Utilizing the same facility for multiple products dictates the need for larger batches and the resultant economy of scale.

IV. SHIFT OPERATIONS

The chemical manufacturing industry has long seen the need for around-the-clock multishift operation.

Initially, batch chemical processing saw a need for extending shift operations beyond one shift operation only when the process needs dictated. However, as the chemical industry and later the API industry extended to continuous operations around the clock, multiple shifts became common often extending to seven days.

Later as the return to batch processing occurred in more recent years, the idea of multishift operation was maintained from an efficiency point of view in order to more effectively use the invested capital in the plant.

There are a number of approaches to scheduling shift work for a five-day around-the-clock operation. The simplest, administratively, is to have people assigned to the same shift routinely. This may be efficient to supervise, but it forces a fixed day, afternoon, and night "crew." Keeping people on a night-only schedule is difficult to sustain, as turnover would be high and would be generally more difficult to maintain from the employee perspective.

This leads to the more common and generally more acceptable three-shift rotating arrangement whereby each week the shift crews are rotated, first from the day to the afternoon and then, the following week, from the afternoon to the night shift. This is a more reasonable schedule that has been used routinely throughout plant operations.

The more administratively challenging schedule is to operate on a 24-hour seven-day schedule. Clearly, this is the most efficient of all schedules because it uses all 168 hours in the week without stoppage. The elimination of stoppage itself is an added efficiency, as there is always some lost time within the scheduled work program whenever a shutdown occurs. As an example, even in a five-day 24-hour operation, at the end of the fifth (and final) workday, there must be some lost time associated with the facility shutdown for the weekend (as well as time lost on the first day of the following week to restart the operation).

The normal "stagger shift" operation I have seen and used involves four "shift crews" that work over three 8-hour shifts. The first beginning at 8:00 a.m. (day), the second at 4:00 p.m. (afternoon), and the third at midnight. The starting times may differ with slightly altered arrangements such as 7:00 a.m., 3:00 p.m., and 11:00 p.m. The principle though is the same. They work full seven days in succession on each shift, with days off between shifts, varying from one to four days. This system, outlined in the table below, operates on a repeating 28-day cycle. Thus, each employee works 21 days out of 28, working one full overtime day per cycle.

Seven-Day Stagger Shift

Crew	1	2	3	4	5	6	7	8	9	10	11	12	13	14
A	D	D	D	D	D	D	D	O	N	N	N	N	N	N
B	A	A	A	A	A	O	O	D	D	D	D	D	D	D
C	N	O	O	O	O	A	A	A	A	A	A	A	O	O
D	O	N	N	N	N	N	N	N	O	O	O	O	A	A

Crew	15	16	17	18	19	20	21	22	23	24	25	26	27	28
A	N	O	O	O	O	A	A	A	A	A	A	A	O	O
B	O	N	N	N	N	N	N	N	O	O	O	O	A	A
C	D	D	D	D	D	D	D	O	N	N	N	N	N	N
D	A	A	A	A	A	O	O	D	D	D	D	D	D	D

D, day shift; A, afternoon shift; N, night shift; O, off

This operational system, or variations of it, is commonly used. Its advantage is that it allows for overlapping coverage for sickness, training sessions, and vacation. Thus if a person is unable to fill his or her shift for any reason, each of the surrounding people works an additional four hours. This permits operation without outside (less experienced) people stepping into an unfamiliar operation. This is important in the manufacture of a regulated drug product where familiarity and understanding of the operation is critical.

More recently, somewhat driven by the issue of energy conservation that emerged during the fuel crises of the 1970s, is a 12-hour shift cycle, one shift starting at 8:00 a.m. and the second at 8:0-0 p.m. This requires four crews that work four days on and four days off.

The example follows:

Four-Day Stagger Shift

Crew	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
A	D	D	D	D	O	O	O	O	N	N	N	N	O	O	O	O
B	N	N	N	N	O	O	O	O	D	D	D	D	O	O	O	O
C	O	O	O	O	D	D	D	D	O	O	O	O	N	N	N	N
D	O	O	O	O	N	N	N	N	O	O	O	O	D	D	D	D

D, day shift; N, night shift; O, off

This shift arrangement requires much more responsibility, as overlapping cannot fill absences, as it would require unacceptable 18-hour shifts. It requires more flexibility to cover vacancies. However, it is viewed as very desirable from the workers' perspective, as it provides long breaks every week.

V. CLEAN ROOM

Today, in the physical plant probably the most significant difference between a traditional chemical facility and an API facility is the "clean room" in the API plant.

This concept, introduced in the 1970s, is derived from the landmark U.S. FDA regulation that established cGMPs. This legislation did not in itself define the need for a clean room, but it essentially required it in order to be in compliance.

Fundamentally the legislation did two things, redefined what a contaminated product is and shifted quality from quality control to quality assurance.

Up until this point in time a "contaminated" product was defined by quality control testing showing that either the material did not meet the specifications or there was seen in the testing the presence of a contaminant. This, of necessity, presumes that contamination is uniformly distributed in the product and that the samples tested are representative of the batch.

This "uniform" contamination concept worked in the cases where contamination occurred in the processing itself and was, therefore, distributed uniformly throughout the product. However, this concept did not deal with "extraneous matter" contamination, where the source was not inherent in the processing but could come from the room environment or the equipment. Often it would not be chemical contamination, as that would easily be picked up by testing. This type of contamination would be random in nature and not subject to normally applied sampling techniques.

Thus, the new legislation defined strict GMPs, which provided detailed rules governing the controls that must be in place in the facility, the equipment, the people, the documentation, and the process. It essentially said that if a factory was found to be out of compliance with the GMP requirements, it could not ensure that any batch of product was free of contamination; hence all batches are declared contaminated regardless of the testing results for any batch.

In terms of facilities the key issue was the common factory environment. It was the practice of isolating the final API in essentially the same environment as all prior intermediates. This potentially exposed the final API product to the same factory environment where extraneous contamination ranging from paint chips from equipment to rust from overhead piping and unfiltered solids from earlier process steps could carry forward into the final product.

The most practical way to meet this new requirement was to provide a separate clean room within the factory where the environment would be subject to higher levels of control than in the normal operating area.

I had the opportunity of overseeing the establishment of the first clean room at Merck's multiproduct plant in Rahway, New Jersey, in the late 1970s. The facility was tailored after a sterile room concept where access was limited and clean uniforms were required with the appropriate hair covers. It had controlled and separated air-handling systems, appropriate wall and floor finishes, no protruding piping or fixtures where dust or dirt could collect, and thorough cleaning procedures.

It was designed to be the finishing room where the final isolation of the API took place and any subsequent finishing steps such as milling, final blending (required for all products), and packaging. Even within this controlled environment, covered containers were used whenever transfer of material was necessary.

The size of the area and the extent of processing that would be carried out in the clean room would be dictated by the process. Logically the best approach would be passing a solution of the product through a fine filter and taking it through a separating wall into the next vessel that is located in the clean room. Normally, most products have a recrystallization step that would fit the need. In the unusual event that recrystallization is not part of the process, then one would go back into the process to a point where a solution of an intermediate exists. That solution once filtered would be brought into the clean room. It would then require all subsequent steps to be carried out in the clean room. This could cause a significant increase in cost to erect an expanded clean room. One should consider whether adding a standard recrystallization to the process could be justified as capital avoidance.

Another significant decision is whether to build a dedicated clean room for each product or minimize capital by having a single clean room for all products at the site. This would be generally cost effective for multiproduct factories, particularly if the products have relatively small volumes. Again, the overall economics would govern.

VI. COST CONTROL

The costs of any business operation must be monitored and controlled. An API factory is no exception. The usual costs incurred can be broken down into a variety of classifications, which I will discuss later.

It is clear that if the plant operates to produce a single product, then regardless of the cost system used, the actual all-inclusive manufacturing costs incurred will be the basis for the product gross margin (PGM), which is the sales revenue minus the actual manufacturing costs. This is straightforward and does not pose special problems.

In a plant, however, where more than one product is made, one must develop a system to allocate the shared costs to the various products. This is not as simple as it sounds and can influence the perception of the profitability of a product.

The first consideration is to determine the fixed and variable costs involved with every product manufactured. Some items are obvious; others are not. A variable cost is directly proportional to the quantity of a product manufactured, such as raw materials and auxiliary chemicals used in the synthesis. For each kilogram of product a specific amount of each raw material is required. If production of that product ceased there would be no expense for that raw material. Similarly the labor used to run the batch is also variable; the labor used is directly proportional to the number of batches run. On the other hand an essentially fixed cost is independent of the quantity of a product made. This would include supervision at the factory level and clean-out chemicals used for turnaround of the equipment. However, there are many classes of costs that have both a fixed and a variable component.

The following examples list typical cost element classes, each as fixed or variable:

Item	Fixed	Variable
Raw materials	None	All
Direct labor	None	All
Cleaning chemicals	All	None
Steam	Part	Part

Electricity	Mostly	Some
Water	Some	Mostly
Waste disposal	Mostly	Some
Quality testing	Part	Part
Quality assurance	All	None
Supplies	Mostly	Some
Warehousing	All	None
Dispensing	None	All

These above costs are always going to be a factor in establishing the overall cost and expense structure for a factory. One normally prepares a budget for a factory on the basis of the expected volumes for each product. This will dictate the total base activity for the estimating of costs for each product.

I strongly recommend that cost standards be developed for each separate process step for each product ideally at each isolated intermediate (although it is not necessary that each step be isolated). The cost standard will include all of the above items, where the variable costs will be essentially the same regardless of volume and the portion of the fixed costs that each step will absorb.

The basis for dividing the total fixed costs among products can be done in any way as long as the total factory fixed overhead is fully accounted for. A common basis is to link the fixed overhead portion to the equipment use time or the direct labor use.

This permits the establishing of cost standards that are useful for production cost control.

The primary variables that should be measured against the "cost standards" for "variances" are

- quantity of product (or intermediate) actually made in the step (variation from standard usually referred to as "yield variance"),
- quantity of auxiliary materials used in the step ("charge variance")
- quantity of labor used for the step ("labor use variance"),
- unit cost of labor ("labor rate variance")
- the number of batches made in the measured time period compared with the basis on which the standard was established ("volume variance"), which results in a different absorption of fixed overhead than expected, and
- the actual costs of fixed overhead that shared by the products is different than originally budgeted ("spending variance").

The pharmaceutical plant has an added cost not common to most other chemical factories. This is the need to carry out detailed and extensive cleaning whenever nondedicated facilities are used. These "clean-outs," often including detailed and laborious methods, materials, and specific testing ought to be themselves the subject of separate cost standards.

There are a number of reasons for the establishment and use of cost standards.

- First to provide a direct and accurate measure of the performance and real cost of each process step in the factory
- Second to provide management with a tool to measure the effectiveness of an operation and an operating group

- Third to allow the process development people with a powerful tool to predict and measure the value of proposed improvements in the cost of manufacturing specific products

This allows management to be able to better judge the value of a process improvement so as to be sure that it is worth undertaking.

A. Fixed Overhead Absorption

In a facility dedicated to a single product there is no question that that product, regardless of product volume, must absorb all the fixed overhead costs. Obviously, as the product volume rises the unit cost of the fixed overhead absorption falls.

In a multiproduct facility this issue is less clear. All of the fixed overhead must still be fully absorbed; however, the mechanism can vary and must be decided on by management. One commonly used method is to determine the total labor cost planned for the year in that factory and divide that into the total fixed overhead absorption required for such a factory. Thus, on the basis of the plan for the year each product independent of the others has a specific total overhead burden to absorb (linked by standard labor used). If the quantity produced is less than the plan, then the product will not cover the entire fixed overhead it was scheduled to cover and generate an unfavorable variance without adversely affecting other products in the factory.

In a multiproduct facility, the impact of one product not meeting its volume projected in the plan does not adversely affect the other products. However, it can have an effect on the cost of the other products in the following year's plan if the reduced requirements for that product are not made up for by increased volumes of the other products it shared the facility with.

Even if the fixed overhead remained the same for the following year, there would be fewer total units of products made at the facility, forcing all of the products to absorb more overhead, thereby raising their apparent costs.

Much of what has been discussed in this section is not unique to API operations but a rational approach to quantifying the real cost of a manufacturing activity.

VII. EMPLOYEE SAFETY

A fact that has added greatly to this issue in an API factory is the increased potency that newer APIs have shown. This is partly offset in the pharmaceutical dosage form, as very small amounts of APIs are required in its pill. However, the API, generated in pure form at the API manufacturer, presents an additional challenge in processing, sampling, and testing operations at that site. It also adds a challenge to the pharmaceutical finished dosage form manufacturer who must handle and charge this material in a pure form to its process. Wearing respirators, air masks, or even full-sealed suits protect when very noxious materials are used or generated that could result in exposure to the personnel.

Here one must have sufficient toxicity data to know the nature of the hazard potential to personnel. Planning for the operation includes preparing for both normal operation, which should limit exposure, and potential deviations in operation that could generate greater exposure. It is essential to be overly cautious when planning for these types of operations.

13 Sterile Bulk Active Pharmaceutical Ingredient Production

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I. INTRODUCTION

This chapter will describe the production of sterile bulk pharmaceutical chemicals. Support for the aseptic processing activities utilized in the production for all sterile materials including active pharmaceutical ingredients (APIs) and excipients is a regulatory requirement (1).

The delivery of parenteral medications as an injection requires that the materials be sterile. With many products, this is readily accomplished by dissolution in water and subsequent filtration through a microbially retentive filter. There are, however, many sterile products in which the API is not in solution including both liquid suspensions and sterile powders. In these products, the API is aseptically filtered while in solution in an appropriate solvent system and then crystallized and processed under aseptic conditions. The sterile solid is then separated from the liquid phase, dried, size modified as needed, blended (if necessary), and then bulk packaged for shipment to a dosage form site for final formulation and/or filling while maintaining its sterility. Penicillins, cephalosporins, and their many derivative products and corticosteroids such as hydrocortisone acetate and prednisolone acetate are typical APIs that must be made sterile prior to formulation into a drug product. Similar processes are utilized for other solids used as formulation additives in sterile products such as arginine hydrochloride and sodium carbonate.

Cephalosporins, penams, and other antibiotics are readily soluble in water at the correct pH; however, their stability in aqueous solution is limited. Sterile formulations of these drugs can be accomplished using freeze-drying; however, a far more economic process is by means of sterile crystallization as described earlier. A hybrid process in which the freeze-drying is performed at the bulk stage followed by milling and subdivision is also in common use.

An emerging method for production of sterile bulk materials is by means of terminal irradiation of the material. Because the final materials will be injected into humans, the last-step production facilities, processes, and controls are nearly the same as those described in this chapter to ensure adequate protection from bioburden, endotoxin, and foreign matter.

II. TYPICAL STERILE BULK ACTIVE PHARMACEUTICALS INGREDIENTS AND EXCIPIENTS

Antibiotics

Penicillin and its derivatives—penicillin G, carbenicillin, amoxicillin, etc.
Cephalosporins—cefazolin, cefoxitin, cephalexin, cephradine, etc.

Penams—meropenam, faropenem, oxapenam, etc.
Monocyclic β-lactams—aztreonam, tigemonan, etc.
Others—polymixin, bacitracin, etc.

Corticosteroids
Hydrocortisone, triamcinolone, betamethasone, etc.

Excipients
Arginine hydrochloride, ascorbic acid, sodium bicarbonate, etc.

III. STERILE SYNTHESIS STEPS

The processes utilized for the production of sterile APIs are generally similar. The chemical reactions used may be exactly the same as those used for the purest oral/topical grade of the same material that is often used as the starting material for the sterile product. The nonsterile bulk material is put into a solution in an appropriate solvent system and passed through microbially retentive filters into a sterile vessel. The material in the sterile vessel is crystallized by pH adjustment and/or solvent/water addition (seed crystals are sometimes used). The resulting slurry is filtered to remove the bulk of the initial solvent and dissolved impurities and washed with an appropriate sterile solvent. The wet solid is dried to remove residual solvent. The dry powder may then be milled (or micronized), blended, and then subdivided into sterile containers. The details of the individual process vary of course with the product, but the basic elements rarely differ.

The greatest challenge in all of this is to adapt the chemical equipment and processes customarily used to the production of sterile materials. This problem is greatest in the latter stages of the process after the crystals are formed. Prior to crystallization, the materials are in solution within sealed reactors, and while any vessel or line downstream of the sterilizing filter must be sterile, that rarely presents substantial difficulties. Once crystals are created, all subsequent steps must be accomplished under aseptic conditions throughout. Filtration equipment, dryers, blenders, and mills must all be sterilized, and the materials must be conveyed from one equipment item to the next by means that prevent contamination. The most evolved approaches use multipurpose equipment such as a Rosenmund Nutrex® or similar systems, which are specifically designed to be reliably sterilized and to minimize the number of transfers required and thus are ideally suited for production of sterile APIs.

IV. CONSIDERATIONS FOR STERILE BULK PHARMACEUTICAL CHEMICAL

The requirements for production of sterile drug products are extensive, and there are numerous texts that can provide insight into the myriad of considerations necessary for success (2,3). None of the processes is subject to greater scrutiny than aseptic processing, and the production of sterile APIs is one of the more difficult of all aseptic processes to properly manage (4). The most important considerations from a sterile product perspective are those that relate to sterility, endotoxin, and foreign matter, each of which requires careful control.

A. Sterility

Foremost of all requirements for sterile products is the maintenance of sterility, throughout the entire process train from the point that the product is rendered sterile. The process control requirements for this are well established in aseptic processing operations. As a minimum they must include the following:

- The sterilization of process equipment, process fluids, wash fluids, vent gases, utensils, operator gowns, and packaging components must be properly validated.
- The processing environment (or isolator) must be specifically designed to preclude the introduction of microbial contamination and it must be decontaminated prior to use.
- The process environment shall be monitored to assess the potential for microbial contamination.
- Personnel working on the process must be adequately trained in aseptic processing techniques, aseptic gown qualified and closely supervised.
- The entire process must be supported by a process simulation study that demonstrates the capability of the facility to produce sterile materials (see later section).

B. Endotoxin

Endotoxins are fever-inducing substances derived from gram-negative microorganisms. The levels of endotoxin present in sterile drugs must be closely controlled, as high levels have been associated with patient death. The use of solvents in processing and cleaning can mitigate some of the concerns relative to endotoxin control; nevertheless, the firm must consider the potential for endotoxin at all times. The methods for control of endotoxin include those itemized earlier for sterility, with some additions as follows:

- Time limits should be imposed on process steps, especially those steps involving process water such as dissolution and filtration.
- Equipment items should be adequately dried subsequent to cleaning.
- Production materials susceptible to endotoxin contamination must be tested prior to use.
- Water systems must be designed, qualified, and controlled to ensure production of proper quality water.
- Water used in the final isolation and purification steps (i.e., steps where endotoxin may be retained), as well as final rinse water for cleaning of the associated equipment, must have an endotoxin limit no greater than that specified for water for injection (WFI).

C. Foreign Matter

Because these materials will be injected, they must be largely devoid of foreign matter. In most sterile products, this control means a focus on the container-closure system and little else because the solution may be filtered just prior to filling/sealing of the container. With sterile bulks, the situation is substantially different. The materials are cleanest right after sterilizing filtration and susceptible to contamination from that point forward. The entire equipment train must be designed, maintained, and cleaned in a manner that minimizes the particle content of the finished product.[a]

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[a] The authors encountered one situation where the requirement for absence of foreign particle matter was considered so vital that the firm considered opening a previously sterilized vessel and rinsing it with sterile filtered WFI to remove any particles present in or dislodged by the steam! Fortunately, this practice was not implemented, given the even greater concern for sterility.

- The equipment train must be subjected to validated cleaning procedures to ensure residues are removed. Cleaning should be performed using automated systems, where possible, to minimize variability in outcome.
- Materials, utensils, and other items must be selected to minimize their particle generation potential. Of particular concern are woven materials likely to cause fibers.
- Cleaning/preparation of containers must ensure their suitability for use.

The control of foreign matter requires some degree of caution; however, it should be recognized that it is not absolute. No practice can assure the absence of particles in all materials. The USP requirements for injections state that injectable products must be "essentially free of visible particles," a circumstance that is virtually impossible to demonstrate especially in sterile powder materials where inspection is largely restricted to examination of the surface (5). In discussion with clients, industry personnel and FDA officials, the consensus is that the expectation is nonabsolute, and while tight limits are expected, some uncertainty with respect to the actual levels of particle present is inherent.

One last consideration must be mentioned with respect to assuring the quality of sterile bulk materials for the aforementioned attributes (and to a lesser extent, the other quality attributes of these materials). Sampling the bulk sterile material to determine sterility, endotoxin content, or particle level must be undertaken with extreme care. The samples must be collected in a manner that does not adversely affect the very properties the sample was intended to evaluate. Contamination control of these materials must be considered with respect to every invasion of the process train, environment, or product container.

The physical parameters of the crystallized materials may be important in subsequent processing. As many of these products are filled as dry powders, the particle size, flowability, static charge, and other powder-handling properties must be well controlled to ensure subsequent success.[b] This concern is common to many APIs, but may be critical in aseptic powder filling where interventions are always problematic.

V. BUILDINGS AND FACILITIES

Facilities for the preparation of sterile APIs must accommodate the very different type and scale of process equipment utilized. The crystallizers, dryers, filter dryers, mills, and other equipment required are ordinarily much larger than the typical equipment used in the preparation and filling of individual sterile dosage form containers. As a consequence, these facilities customarily resemble API plants more than sterile production sites. Ceiling heights are greater and processing rooms much larger to accommodate the API equipment. The use of solvents in the process will mandate explosion-proof equipment throughout. The facility areas accommodating the process train elements outside the aseptic core may be almost indistinguishable from standard API processing areas, with somewhat greater attention to microbial and particle control despite the fact that the materials are not yet sterile.

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[b] Differences in particle size from clinical/proof of concept lots to commercial-scale production were responsible for extreme difficulties with weight control for one sterile dry powder. When the crystallization process was modified to once again produce the same material characteristics, powder filling proceeded without difficulty.

A. Critical Areas

The core of the sterile API suite utilizes materials and finishes essentially identical to those used in aseptic filling facilities. As previously discussed, aseptic operation is required from the point at which the product stream is sterilized, usually by sterile filtration in solution. While crystallization may often be carried out in a pre-sterilized closed vessel, the subsequent steps of filtration, drying, and sometimes milling present more problems in attempting to maintain sterility. With the exception of specially designed multifunctional equipment such as the previously cited Rosenmund Nutrex, designed to isolate and dry sterile powders within a pre-sterilized vessel, these operations must occur within an aseptic environment. Spray drying has also been successfully utilized for the production of sterile antibiotics enabling the transition from solution to dry powder in a single unit operation.

There are two prevalent designs in use to carry out aseptic operations, reflecting the differences in filling technologies currently utilized for sterile dosage form production. Older facilities utilize manned clean rooms with highly purified air supply (class 4.8 through 7 per ISO Standard 14644), with personnel gowned for aseptic processing. Some newer facilities have incorporated isolation technology for increased product protection.

1. Manned Clean Rooms

The majority of the aseptic core (the area directly adjacent to where sterile materials will be exposed) maintains ISO class 7 conditions during operation and ISO class 6 at rest. These conditions comply with EU GMP annex 1 grade B conditions as required for aseptic processing (6,7). Localized ISO class 4.8 environments with unidirectional airflow (EU annex 1, grade A) are utilized for the essential aseptic operations such as seed introduction; material sampling, and subdivision into bulk containers (Fig. 1).

2. Isolator Based

These facilities use an ISO class 8 (or better) background environment, with aseptic isolators at all locations where the sterile materials can be exposed to the environment (8). The isolators provide an unparalleled certainty of separation between personnel and the product (Fig. 2).

B. Closed and Open Systems

World-class production of sterile APIs utilizes “closed” systems for the entire process to protect the materials within the aseptic core. Parenteral Drug Association (PDA) Technical Report 28 originally defined closed systems in 1998, and this was altered slightly in the 2005 revision to clarify the requirements. The PDA report defines a closed system by the performance attributes it is expected to maintain (9):

- “Is constructed, installed and qualified in a manner which demonstrates integrity is maintained throughout the full range of operating conditions,

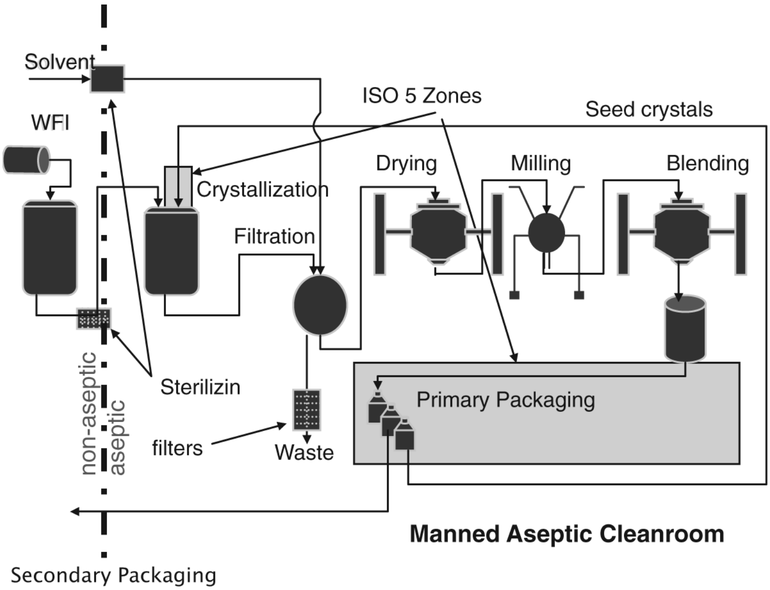
Solvent
WFI
ISO 5 Zones
Seed crystals
Crystallization
Drying
Milling
Blending
Filtration
non-aseptic
aseptic
Sterilizin
filters
Waste
Primary Packaging
Manned Aseptic Cleanroom
Secondary Packaging

FIGURE 1 Typical sterile API cleanroom process.

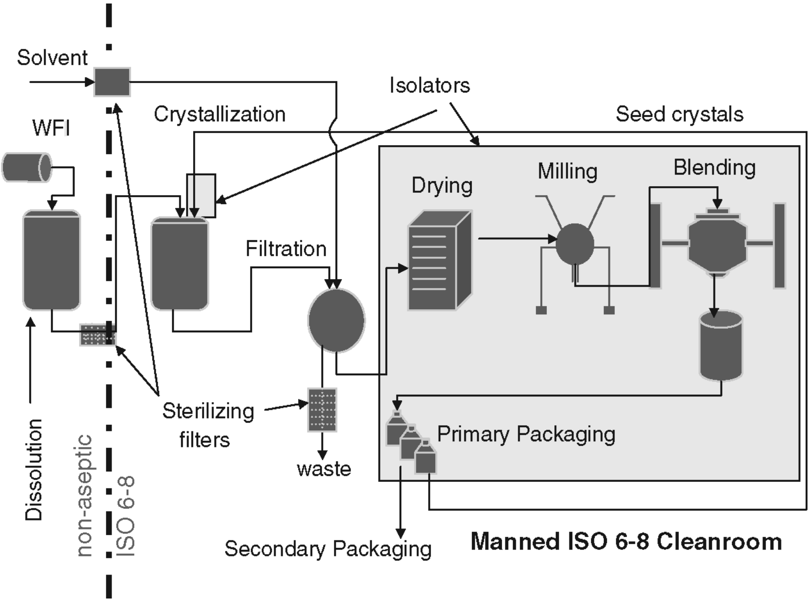
Solvent
WFI
Isolators
Crystallization
Seed crystals
Drying
Milling
Blending
Filtration
Sterilizing filters
waste
Dissolution
non-aseptic
ISO 6-8
Primary Packaging
Secondary Packaging
Manned ISO 6-8 Cleanroom

FIGURE 2 Typical sterile API isolator process.

and over a time period inclusive of the longest expected usage (i.e., manufacturing campaign). The qualification is done according to a formal protocol, following generally accepted engineering principles, and is documented.

- Is sterilized-in-place (SIP) or sterilized while closed prior to use using a validated procedure.
- Can be utilized for its intended purpose without compromising the integrity of the system.
- Can be adapted for fluid transfers in and/or out while maintaining asepsis.
- Is connectable to other closed systems while maintaining integrity of all closed systems (e.g., Rapid Transfer Port, steamed connection, etc.).
- Is safeguarded from any loss of integrity by scheduled preventive maintenance.
- Utilizes sterilizing filters that are integrity tested and traceable to each product lot for sterilization of process streams."

In the best of these designs, gowned personnel are never located in the same environment as sterile product and packaging materials, as the process utilizes closed systems throughout. The use of closed systems for the liquid-handling portions of the overall process train is relatively easy to accomplish (Fig. 3). The tanks, sterilizing filters, and other wetted equipment are easy to close, as they are ordinarily utilized while closed. These equipment items are only opened for cleaning (if required) and maintenance activities. Once the process transitions from the liquid to powder handling, maintaining a closed system is more difficult. Powder-handling and -processing equipment is rarely pressure rated and is ordinarily incompatible with sterilization-in-place (SIP) procedures. The preferred option is to place this equipment in isolators to satisfy the closed system objectives. The equipment in these installations is sterilized in conjunction with decontamination of the isolator in which it is located. The sterilization of product contact surfaces within the isolator must be validated (see the following text). In cases where process equipment is not located within isolators, the process cannot be considered closed and gowned personnel are required for its operation.

Regulatory acceptance of a closed system is not ensured on the basis of conformance with the PDA's definition. In its review of the 1998 version of Technical Report (TR) 28, the FDA explicitly noted, "...that all of the aseptic processing difficulties with sterile bulk pharmaceuticals has been with systems that were 'closed'." Whether that experience preceded the TR 28 definition issuance is uncertain, but certainly caution is warranted. A great deal of the regulatory caution is derived from an earlier perspective (stated in a 1994 PhRMA position paper) that if a system was fully closed, then a supportive process simulation was not required (10). Requirements for supportive process simulation for closed systems was recommended in the 1998 PDA guidance and explicitly stated in the 2005 version.

Typically closed systems & processes

- ❖ Dissolution
- ❖ Reaction Step(s)
- ❖ Sterile Filtration
- ❖ Seed Crystal Addition
- ❖ Crystallization

Typically open systems & processes

- ❖ Filtration/ Centrifugation/ Washing
- ❖ Drying
- ❖ Milling
- ❖ Blending
- ❖ Bulk Packaging

FIGURE 3 Closed & open system usage.

Barrier and other designs in which all of the attributes associated with closed systems are not present are considered "open" and acknowledged as less capable. Systems that are not closed are still in use across the globe, but given the clear regulatory expectations, more and more new systems are using closed isolator technology in the later stages of the process train where powder handling occurs.

C. Supportive Clean Areas

1. Dissolution Area

The aseptic portion of the sterile bulk production is commonly supported by two very different environments. The nonsterile production materials are processed in pressure-rated vessels in which solvents and other items (e.g., amorphous carbon for impurity and color removal) may be added. The use of solvents mandates an explosion-proof environment for these activities and, thus, is often separate from that utilized for the other preparation processes. The processing environment in which the dissolution is carried out is usually ISO class 8 (class 100,000) during operation but may require an even cleaner environment depending on the firm's risk assessment.

2. Preparations Area

The items utilized in the aseptic core are prepared in an ISO class 8 environment (with localized ISO class 5 to control particle counts over selected activities). In this area, items are readied for sterilization/depyrogenation through double door units that can be later unloaded from inside the aseptic core. Airlocks and/or pass-throughs are frequently utilized to facilitate the transfer of sealed sterile bulk containers from the core. Final packaging and labeling may also be performed in this area. Wash areas for utensils, wrapping stations, spare parts, and other support systems are located within the preparations area.

D. Colocation of Bulk Manufacturing and Dose Filling

A limited number of sterile API production facilities have been constructed as a single aseptic suite incorporating both sterile bulk manufacturing and final dose filling capability. Colocation within a single suite can reduce the capital expenditure, as many of the infrastructure and support systems can be shared. Where this choice is made, it is more prevalent to ship or transfer the crude bulk API from the API manufacturing facility to the dosage form facility where the final dissolution, purification, and isolation take place. In this manner, the firm avoids shipping of sterile bulk and its concomitant package integrity issues.

VI. PERSONNEL TRAINING AND QUALIFICATION

Personnel working in conventional manned sterile API facilities must have comparable skills to other aseptic operators. They must be proficient in aseptic gowning, aseptic technique, as well as the process skills required of chemical synthesis operations. The methods and the equipment utilized in sterile API production are substantially different than those in small container filling, and operator job training must be adapted accordingly. Where isolation technology is utilized for the later stages of the process, there is a reduced need for aseptic proficiency; however, the operators must now be cognizant of the intricacies of isolator operation.

VII. CONTAINER-CLOSURE SYSTEMS

Sterile bulk materials are unique in that most finished bulk containers will exit an aseptic core (or isolator), be labeled and final packaged, warehoused, shipped (perhaps globally), and later introduced into the critical zone at another aseptic facility. This places extraordinary demands upon the packaging system, and the best package designs provide maximum protection of the product throughout its shelf life. Equally important are the practices and methods utilized for sterilization, initial filling and sealing of the containers at the manufacturing site, as well as the dispensing of the sterile material at each of the filling sites. The container-closure system is inexorably tied to the equipment and procedures utilized to sterilize, transfer, and fill the containers and closures and thus has substantial impact on the facility design as well as the integrity of the aseptic process. This must include means for taking samples for sterility and other tests in a noninvasive manner during the filling and sealing process. Careful attention should be given to the design of the container. The preferred system from a shipping/storage perspective may not be the easiest to fill or discharge from. The choice of a sterile bulk packaging system must consider all aspects of use from preparation, through filling, sampling, and ultimate discharge. Presented in the following are brief descriptions of the primary packaging systems utilized for sterile bulk materials, along with the key advantages and disadvantages of each.

A. Glass

The first container employed for many sterile bulk materials is often a glass vial with conventional stopper, as the initial scale of production may be so small as to preclude the use of a larger package. A scaled-up design would be a wide-mouth screw-capped jar, with tape providing an additional layer of security. This has the advantage of being easily sterilized and/or depyrogenated, impervious to moisture, and relatively inert, and can be inspected while still closed. Negatives include uncertainties of seal integrity, difficult protection of the components post sterilization, and susceptibility to physical damage. Heat- or twist-sealed, sterilized low-density polyethylene (LDPE) overwrapping can be added to simplify introduction into the aseptic filling suite. Custom-designed shipping containers are often added to enhance the container integrity during shipping. This packaging system is more likely to be used in early development and replaced as the scale of operation increases. It is less commonly utilized in commercial operations.

B. Aluminum/Stainless Steel

The original model for containers of this type is the milk can once so common in the dairy industry. These metal containers rely on an elastomeric closure to seal the lid to the body of the container. The lid can be secured with a wire or a lever system to ensure its integrity. The containers and lids can be of either a single-use (aluminum) or a multiple-use (stainless steel) design. Advantages are ease of sterilization/depyrogenation, greater moisture and light protection, and physical strength. Disadvantages include the inability to inspect the contents, awkward protection post sterilization, and large opening size. Reusable stainless steel cans that were once almost universal have been largely supplanted by single-use aluminum cans to reduce cost and weight. Additional layers of sterilized LDPE are added over the closed container to facilitate entry into the aseptic core at the filling site. Fiber drums or other protective containers are sometimes provided as an outermost layer during storage and shipping.

C. Plastic/Laminate Bags

The use of ultraclean sterilized LDPE (or other plastic) is a common package selection. The bag in contact with the product can be heat sealed or twist sealed (with a surrounding heat-sealed bag). Heat sealing of the product contact bag risks charring of material in or near the seal area as the seal is being formed. An internal vacuum or pressure can be utilized to provide a direct indication of container integrity to the end user. Additional bags with laminate layers to eliminate moisture or light penetration are commonplace. The completed multilayered package is shipped in corrugated boxes or fiber drums. Advantages include low cost, low weight, and ease of inspection (provided a laminate is not present). Among the disadvantages are the absence of structural strength, potential static charge, and risk of product charring in the heat seal. Package integrity during air shipment can be ensured through qualification of the heat sealer. An “endless bag” concept has been successfully utilized by many firms to reduce exposure of the sterile powder to the surrounding environment (Fig. 4).

D. Sterility/Product Samples

The preparation of a sterile API includes the collection of sample materials for sterility and other tests. These samples must be obtained from the batch in a representative fashion that ensures the validity of the sample and yet maintains the sterility of the materials. Some adaptation of the product package is often used to collect samples in a manner that provides this confidence. It should be recognized that opening/accessing the sterile bulk containers to collect samples represents an unnecessary risk and is to be avoided. The use of a single composite container inserted into the subdivision process for sample collection is only slightly less risky. The preferred approach is to collect samples at intervals during the process and composite/subdivide them for the various tests in a well-controlled ISO class 5 environment with unidirectional airflow.

VIII. TIME LIMITATIONS

Aseptic processes often utilize time limits on process steps prior to sterilization to preclude excessive bioburden in the filtration process, as well as prevent endotoxin from becoming a problem. Sterile bulk pharmaceutical chemicals are no exception, and appropriate time limits should be validated on the dissolution and filtration steps to provide the required controls. Time limitations are also

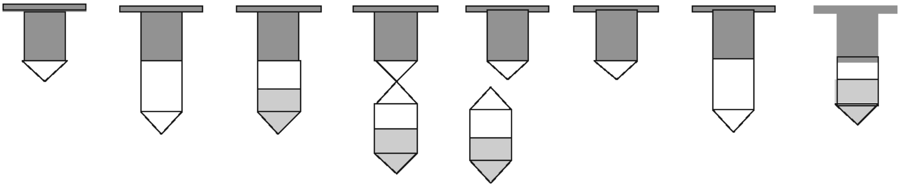

FIGURE 4 Endless bag filling.

imposed on the length of production campaigns between sterilization of the process train.

IX. ASEPTIC PROCESSING SIMULATION

The successful production of sterile bulk materials requires close integration of two very different production modes: bulk pharmaceutical chemicals and aseptic processing of sterile materials. In the combination necessary for preparation of sterile bulks, neither of the core processes is significantly changed, but certain adaptations are necessary to accommodate the requirements of each.

Establishing the sterility of aseptically processed sterile drugs is one of the more difficult, if not the most difficult, tasks in the industry. As there are no direct means by which the sterility of aseptically produced materials can be determined, firms utilize a number of measures to support their practices. Solution drug products are supported by such practices as sterilization validation for components; filter validation for the production solution; environmental monitoring of air, surfaces, and personnel, sterility testing; and process simulations. The situation is really no different for sterile bulk pharmaceutical chemical manufacturing. On one level, the only difference appears to be the size of the container being filled. In practice, because the sterile materials undergo a phase change after sterile filtration from liquid to solid during the process, it is substantially more difficult to simulate a sterile bulk process. In solution manufacturing, liquid media are utilized in the process simulation as a direct replacement for the product formulations. Substitution of the media into the API simulation is typically complicated by the presence of both liquid and solids handling equipment in the process train for the sterile API. The use of a single material (liquid or solid) from the point of sterilization (typically 0.2-μm filtration) to the end of the process is uncommon. Solids cannot be easily handled through the beginning (liquid portion of the process), while liquids are difficult to process in the later (powder-handling) parts of the process.

The regulatory expectations for sterile API production have been the subject of a rare direct interchange of views between the FDA and the industry. The PDA and PhRMA developed an industry guidance document that defined process simulation practices and methods (11). This document enjoyed only limited success. While it was warmly received by the industry, the FDA found several elements objectionable. Concerns were raised regarding the definition of closed systems, requirements for simulation of closed systems, sampling of materials, and other matters. When these comments were reviewed by the task force that had developed the industry guidance, the technical report was revised and a meeting with the FDA requested. Unfortunately, the meeting was never held, and the revision process to TR 28 was suspended for almost five years. In 2004, due to continued issues of contention between the industry and the FDA, a further revision of the technical report was developed (9). That document defines expectations in a manner that seemingly satisfies both industry and regulator alike.

A. Process Simulations

As process simulation studies for sterile bulk pharmaceuticals have been addressed in the literature, only a brief review will be presented herein. The reader is advised to read more focused efforts on process simulation and the closely related subject of SIP to obtain greater insight (12,13).

1. Study Design and Rationale

The firm must develop a supportive rationale for its process simulation studies that outline the assumptions and choices made in the design of the simulation. The primary considerations in the development of the rationale are as follows:

- Materials/media sterilization/entry
- Frequency and number of runs
- Duration/size of runs
- Simulation methods (comprehensive/unit operations based)
- Test material selection (liquid/solid/both)
- Interventions (inherent/corrective)
- Testing/microbial recovery
- Incubation/inspection
- Interpretation of test results—The acceptance criteria for sterile bulk process simulation was first defined by the PDA (11). The basis of the criteria is that the sterile bulk will ultimately be filled into final containers and was set at a maximum contamination level in the bulk simulation that projected to less that 1 CFU per 10,000 filled final product containers.

2. Campaigns

The use of campaigns in which a series of batches is produced following sterilization, with or without intermediate cleaning, is quite common in sterile API production because of the length of time required for complete cleaning and sterilization of the process train. In campaign operations, only very limited cleaning would be performed between lots. Sterilization of the equipment, decontamination of the environment, and removal, cleaning, and sterilization of small items are not performed between batches. Production may not be continuous over the time period (i.e., days or shifts without production are possible).

In campaign operations, the following situations are commonplace and supportable by appropriately designed process simulations:

- Multiple product lots of the same product can be manufactured.
- Container fill volume may change during the campaign.
- Campaign lengths substantially greater than one day are customary.

X. STERILIZATION

The process train for the production of sterile API should be subjected to a validated sterilization processes. The most widely used method is steam SIP. SIP is best suited for the closed portions of the system that often coincides with the liquid portions of the train, as the equipment for those steps is ordinarily both vacuum and pressure tight. The caveats stated earlier for closed systems are only the beginning of the requirements for a successful steam-in-place system design. Other sterilization methods for closed systems have also been utilized, including formaldehyde and peracetic acid; however, these are more difficult to validate than steam and, as a result, have been viewed with some skepticism by regulators (1,4). Dry heat has been successfully used for sterile APIs where the conversion from liquid to solid is accomplished by spray drying. Vaporous hydrogen peroxide has been successfully utilized for process equipment where the materials are in powder form, and isolators have been used to protect that portion of the process.

In order to produce a sterile API, sterilization of many smaller items may be required. Tools, sample containers, environmental sampling materials, and other items must all be available for use in the process. Sterilization can be accomplished by any of the common methods, including steam, dry heat, ethylene oxide, or radiation. Most importantly, the container-closure system utilized for the sterile bulk must be sterilized. Provision should be made in all of these processes to ensure that the items can be introduced into the environment in a manner that minimizes the risk of microbial ingress. This may entail multiple layers of protective materials that protect the items from the sterilizer to the point of use.

The last sterilization element is the sterilizing filter used for the liquid product in solution. The validation of filtration, and all of the other sterilizations required for the process, is essential. The reader should consult texts on sterile processes for information on the validation of these sterilization processes (3).

Depyrogenation of equipment is accomplished by a variety of means, including caustic washes, WFI rinses, and other methods appropriate for the items and equipment being treated. Once depyrogenation has been accomplished, it is important to control the exposure of product contact surfaces to the surrounding environment.

XI. LABORATORY CONTROLS

A. Environmental Monitoring

The conduct of an aseptic process must be supported by environmental monitoring that assesses the conditions during the process. In the liquid portions of the process train, this monitoring is restricted to the surrounding environment; thus the results are not indicative of material impact. In open systems, normally associated with the powder subdivision steps, the environmental conditions must be carefully controlled to protect the product quality attributes. The practices required are essentially identical to those defined for final dosage forms. The single biggest caveat is that the presence of fine powders of antibiotics can inhibit the growth of microorganisms in viable samples and interfere with nonviable particle counting as well. The monitoring systems must be adapted to ensure that the results of the monitoring are valid.

B. Sterility Testing

The performance of sterility testing for sterile APIs presents no unusual hurdles. Aside from the need to inhibit an antibiotic's antimicrobial activity in order to conduct a valid test, the test is performed in accordance with standard practices. The obtaining of samples for the testing was discussed in conjunction with the selection of the bulk container and should be performed in a manner that does not compromise the integrity of the materials, in either the bulk container or the sample itself.

C. Chemical Testing

Samples for chemical and other testing should be obtained in the same manner as those for sterility.

XII. STERILE EXCIPIENTS

The processes, facilities, and controls described earlier may also be utilized in the production of sterile excipients that are necessary in both sterile suspensions and powders for maintenance of drug properties in final formulation. The excipients produced in this manner are generally simpler in structure than the typical API, but their preparation in an aseptic manner requires the same types of controls described previously to ensure sterility and absence of endotoxin and foreign matter. Many cephalosporin products are formulated with an excipient that helps provide optimum pH after reconstitution. The blending and milling of sterile APIs with the excipient is customarily performed at the sterile API production site, introducing additional equipment and unit operations to the overall process. These steps require the same attention to detail as the more complex crystallization processes themselves.

XIII. IN-PROCESS STERILIZATION OF BULK APIs AND EXCIPIENTS

In the preparation of sterile dosage forms, preference has always been given to terminal sterilization over aseptic processing, because of the substantially greater safety associated with materials that are sterilized in their final container. There has always been some consideration given to sterilization methods for bulk APIs that would obviate the difficult sterility assurance issues inherent with aseptic processing. Dry-heat and radiation sterilizations are the methods of choice for in-process sterilization of bulk materials (14). A newer method for establishing an effective sterilizing dose using radiation called VDmax may allow for the use of lower radiation levels while assuring appropriate levels of sterility assurance (15). This may lead to increased usage of radiation as an in-process treatment at the bulk stage. Where these processes are utilized, they typically follow crystallization, filtration, washing, and drying under near aseptic conditions that can help provide control over both endotoxin and foreign matter. The facilities utilized for these processes approximate those described earlier, albeit with slightly less concern for microbiological control.

XIV. OTHER ATTRIBUTES

An important consideration in the production of all of these materials, APIs and excipients alike, is the assurance of appropriate physical and chemical properties not associated with sterility, such as particle size, crystal morphology, impurities, residual solvent, and potency. These are important considerations for any product and should not be ignored. Sterility-related concerns may seem more critical, but attention must be directed toward the other quality attributes of the materials as well.

XV. CONCLUSION

The production of sterile bulk pharmaceutical chemicals represents perhaps the most difficult of all aseptic processes. The complexity and size of the equipment train, the large openings of the bulk containers, and the predominantly manual tasks associated with the more critical operations during the final subdivision of the material all serve to make this process a significant challenge to any firm. Assuring sterility and absence of foreign matter are the most significant challenges. From a chemical processing perspective, the issues with sterile bulks are essentially identical to those of nonsterile APIs, including impurity profiles, degradants, trace solvents, loss on drying, crystal morphology, and particle size. The methods described provide some rudimentary guidance to the practitioner, who must be knowledgeable in the unique aspects of bulk chemical processes, sterilization, and aseptic processing.

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14 Biological Production of Active Pharmaceutical Intermediates

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I. INTRODUCTION

A large number of commercially important compounds are produced by microorganisms employing a process called fermentation. Although a strictly defined fermentation process is anaerobic, many commercial fermentations are aerobic, obtaining energy for cell growth from substrate and oxidative phosphorylation. These aerobic processes, including those of cell culture, will be the focus of this chapter.

A fermentation process consists of three distinct stages as illustrated in Figure 1.

The first stage consists of inoculum development—the cultivation of the desired microorganism to a concentration sufficient to inoculate the second stage, production. During the production stage, the cultivation conditions are orchestrated in a manner that allows for efficient synthesis of the desired product. The third stage consists of harvesting the fermentation broth, after which, the desired product is isolated and purified. Although the fermentation process appears to be rather straightforward, many fermentation parameters must be appropriately addressed to develop a productive, scaleable, consistent, economical, and safe process.

II. MICROORGANISMS

The group of microorganisms commonly employed in commercial fermentations consists of unicellular and filamentous bacteria as well as yeast and filamentous fungi (Table 1). Although these microorganisms as a group are very small in size, they do exhibit different cell properties. The importance of these properties will become more apparent as the fermentation process is fully described. For a microorganism to be commercially important it must not only synthesize the desired compound at economical levels, but it must also be stable at manufacturing scale, for example, after many generations.

As alluded to previously, a successful fermentation process requires that the cultivation broth be contamination free throughout the fermentation cycle. Thus, it is imperative that the starting culture be pure. One approach to ensure purity is to streak a small amount of the culture on the surface of a solid growth medium, incubate at the appropriate temperature until isolated colonies appear, and aseptically transfer an isolated colony to growth media for establishing both the master and working cell banks. Traditionally, these cell banks are prepared in small vials and stored at low temperatures, –70°C, to preserve their genetic integrity.

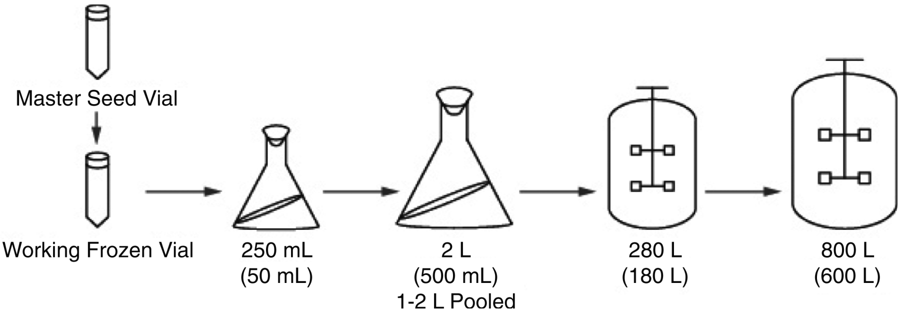


FIGURE 1 "Typical" fermentation process.

TABLE 1 Cell Properties

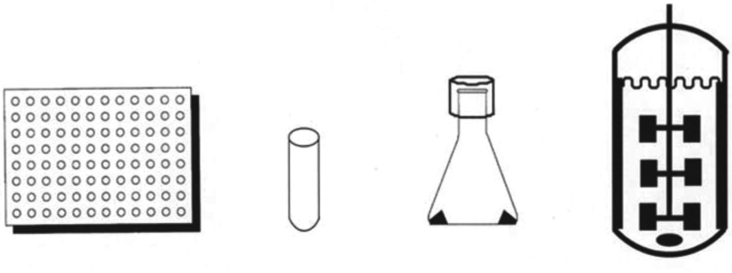
	Bacteria	Yeast	Fungi	Streptomyces
Size (μ)	0.5–2	2–5	5–50	2–30
Shape	Rods, spheres	Ellipsoid spheres	Mycelia, pellets	Mycelia, pellets
Volume (μ^3)	1–10	10–100	Multicellular	Multicellular
Weight (g)	10^{-12}	10^{-11}	Variable	Variable
Doubling time (hr)	0.25–2	0.75–4	3–8	2–8

The *master cell bank* and *working cell bank* concepts were developed to ensure a genetically consistent starting inoculum for large-scale production. A master cell bank of individual frozen vials is created from a validated culture source. Working cell banks are then created from an individual master cell bank vial by culture expansion. Many vials from a single expansion (often involving no more than two to four discrete stages of inoculum development) are created and frozen. Individual working cell bank vials are the starting inocula for each seed train, leading to inoculation of production-scale fermentors, ensuring minimum genetic variation from the original master cell bank. The number of master cell bank vials prepared should be sufficient to provide support throughout the "life" of the product. However, if an improved culture is isolated or produced after product launch, new master cell bank vials will be required.

An improved inoculum development method that still maintains genetic integrity will be presented later, utilizing working cell banks prepared in 2 to 5 L bags (1) containing microbial cells that have been grown under highly controlled conditions. The number of working cell bank vials prepared from a single master cell bank vial depends on the knowledge base of genetic stability. If the microorganism is genetically stable, expansion of the master cell bank through as many as four stages may support production of thousands of working cell bank bags. However, until genetic stability is established, it is prudent to limit the number of expansion stages used to prepare the working cell bank bags. Once established, both cell banks must be thoroughly tested for the presence of contaminating microorganisms. The stability of the cultures during storage is very important and is monitored by statistically testing cell viability after specific storage periods.

III. BIOREACTORS

A number of small-scale bioreactors may be used to cultivate microorganisms, including those shown in Figure 2.



Vessel:	96 Well Microplate	Test Tube	Shake flask	Fermentor
Working volume:	0.05 to 0.2 mL	1 to 10 mL	15 to 500 mL	0.5 to 40 liters
Vessels per day:	1,000 to 10,000	100 to 1000	25 to 100	2 to 6

FIGURE 2 Small-scale fermentations.

The microcell plates and test tubes are usually not part of a fermentation process but can be valuable in studying the microorganism, such as identifying its nutritional requirements. However, the shake flasks and small fermentors can indeed be part of the inoculum development scheme as will be discussed later. In addition, these small bioreactors are highly useful in developing and optimizing certain fermentation parameters, such as medium composition. The first scale-up of a shake-flask fermentation process is usually conducted in laboratory fermentors that are highly instrumented, ranging from 0.5 to 40 L in volume. These fermentors are required to determine the effects of such environmental parameters as aeration, agitation, temperature, and pH on cell growth and product yield. They are very useful for optimizing the fermentation parameters that are not sensitive to scale-up. A special effort must be made to prevent excessive wall growth (an accumulation of cells and fermentation broth on the interior wall of the fermentor above the liquid level) from occurring during the fermentation cycle. Failing to do so will invalidate the results. Wall growth can be greatly reduced by adding Junlon (a polyacrylic acid) at approximately 1.0 g/L (2). Also, 30 and 40 L laboratory fermentors are especially useful for conducting fermentations that experienced excessive wall growth in smaller fermentors.

IV. FERMENTOR DESIGN

Since stirred tank fermentors were introduced into widespread use after World War II, they usually conform to standard design ratios. These ratios are shown in Table 2. One important design aspect not usually mentioned is the amount of headspace above the fermentation liquid that should be allowed. A larger headspace is useful for containing foam that often results from the aeration of the medium. A typical ratio of headspace to the fermentor tank height of 0.33 will contain many foaming broths. Sometimes the physical height of the fermentor may have to be limited by building height constraints if a fermentor is added to an existing building. Probes, air outlet condensers, and other services

TABLE 2 A Summary of Some Published Stirred Tank Fermentor Design Configurations

Reference	3	4	5	6	7	8
Height of liquid to diameter of tank	1.0	1.0 small scale 2.0 pilot scale 2–5 industrial	1.0	1.0	1.0–1.6	2.0–5.0 industrial
Diameter of impeller to diameter of tank	0.34	0.3–0.5	0.33	0.33	0.34–0.5	0.3–0.5
Height of bottom impeller off base to impeller diameter	0.8–1.0	0.08–0.10	1.0	1.0	0.7–1.4	–
Space between impellers to impeller diameter	1.0–1.2	1.0–1.2	–	–	1.0–1.3	–
Baffle width to tank diameter	0.03	–	0.1	0.03	0.08–0.1	0.07–0.1
Top impeller distance below liquid height to impeller diameter	–	–	–	–	0.5–1.0	–

are usually attached to the top of the tank, requiring space above the fermentor, and may limit overall tank height.

Impeller design is of considerable importance to the optimal operation of fermentors. The correct impeller for a given situation is determined by the fermentor geometry and the nature of the fermentation. It is relatively easy to change impellers on the impeller shaft, and this gives multiuse fermentors some flexibility to cater to the needs of individual fermentations. Although there are many impeller designs to choose from, impellers can be separated into two major types, axial flow impellers, which pump liquid up or down the fermentor, and radial flow impellers, which pump liquid radially outward to the edge of the fermentor. Some impeller designs generate a mixture of the two actions. The impellers must perform two functions during the fermentation. At the bottom of the fermentor, where air enters, the impellers must create high shear to break up bubbles to prevent slugging and to create small bubbles to maximize gas mass transfer interfacial area. For this reason a high-shear flat-bladed turbine, known as a Rushton impeller (9–11), may be added at the base of the fermentor over the air inlet ring. Traditionally the other impellers above this may be curved-bladed turbines or other axial pumping designs to circulate fluid around the fermentor vigorously. Today impeller manufacturers and mixing experts offer a range of impellers even more optimally designed for specific fermentations (12). One of the major considerations when selecting such an impeller set is the viscosity of the fermentation broth and its non-Newtonian physical characteristics.

Air sparger designs vary, but a sparger is typically a tube formed into a circular shape. It has a series of fine holes drilled into the tube to let the inlet air into the fermentor. The size of the holes is important. If the holes are too small, a large pressure drop ensues, and if they are too large, the bubbles created are too large and may coalesce to form slugs. Holes of 0.5 mm are serviceable, but it is important to have the holes facing down to the bottom of the fermentor so that falling solids, for example, cells or medium components, will not block the air inlet holes. The diameter of the circular shape of the sparger should be designed to match the impellers. The air should be made to come out directly under the impeller blade tips, which is the area of the highest shear, to ensure that the bubbles are formed with maximum interfacial surface area.

TABLE 3 Typical Impeller Speed Ranges as a Function of Fermentor Volume

Fermentor volume (L)	Typical impeller speed range (rpm)	Number of impellers
3	200–2000	Single
10	200–1200	Transition
50	100–800	Transition
200	50–400	Multiple
500	60–300	Multiple
10000	25–200	Multiple

Source: From Ref. 6.

TABLE 4 Typical Fermentor Aeration Rates

Fermentor configuration	Fermentor size	Aeration rate (vvm)	Reference
Stirred tank	Laboratory	0.7–1.0	8
Stirred tank	Laboratory	1.0	3
Stirred tank	Large scale	0.2–0.5	13
Stirred tank	23,000 L	0.2–0.3	8
Airlift	1500 m^3	1.6	14

TABLE 5 Typical Fermentor Power Input

Fermentor description	Fermentor volume (L)	Power input (kW/m^3)
Laboratory	<10	8–10
Pilot plant	10–500	3–5
Plant	>500	1–3

Source: From Ref. 5.

Normal operating conditions for a fermentor depend on the exact fermentation and the process control objectives undertaken during the fermentation. Typical ranges of impeller speed, power input, and aeration rates are shown in Tables 3 to 5. All the variables, impeller speed, power input, and aeration rates, vary strongly with fermentor size, particularly power input. At a very large scale (>100,000 L), the power input per unit volume drops considerably and the practical motor size and heat generation may be the factors that limit the fermentor operating conditions. At a very large scale, heat removal is a considerable consideration. Aeration rates are typically reported in volumes of air per volume of medium (vvm), which is the volume of air per volume of fermentation liquid broth per minute. Mild agitation results from power inputs of 0.2 to 0.8 kW/m^3 and strong agitation from 0.8 to 3.0 kW/m^3 (13).

An important aspect of fermentor operation is to have a condenser on the top of the fermentor gas outlet. This serves two functions: it prevents significant evaporative water losses from the fermentation broth, and it also dries the air to prevent the air outlet filters from becoming wet (and hence more susceptible to being a contamination source). The water-holding capacity of air varies significantly with temperature (Table 6).

If a 1000 L fermentor operating at 30°C, 1 vvm of aeration, and dry inlet air, did not have an air outlet condenser, then

$$\begin{aligned}\text{Maximal water loss} &= 1\ \text{m}^3\ \text{air/min} \times 30.4\ \text{g water/m}^3\ \text{air} \\ &\quad \times 60\ \text{min/hr} \times 24\ \text{hr/day} \\ &= 44\ \text{L/day, or } 4.4\%\ \text{volume loss per day}\end{aligned}$$

TABLE 6 Water Content of Saturated Air

Temperature (°C)	Water content of saturated air (g H_2O/m^3)
5	6.8
10	9.4
15	12.9
20	17.3
25	23.1
30	30.4
40	51.3
50	83.2
60	130.3
70	198.0
80	292.3
90	420.1

Source: Data from Psychrometric Tables, Universal Industrial Gases, 2009.

Such volume losses are not sustainable over a long (e.g., 10 days) fermentation. This is also a significant issue in shake-flask fermentations, where evaporative losses can be considerable. Product or cell mass data can be considerably overestimated if evaporative losses are not accounted for, as shake flasks do not come equipped with condensers. It is also important when using shell and tube condensers on the top of fermentors that the cooling water enter at the bottom and leave at the top, as if the reverse configuration is used, air bubbles can get trapped in the condenser and decrease the effective heat transfer area.

Power input calculations can be important to size the fermentor motor and to consider when the microorganism is very shear sensitive or when the broth is very viscous. The classic power consumption curves for impellers were first described by Rushton et al. For the turbulent flow required in fermentors without any gas flow (13):

$$\frac{P_o = N_p N^3 D_i^5 Ro}{(g_c.60^3)} \tag{14.1}$$

where P_o, power drawn by ungassed impeller (W); N_p, power number, a constant under given conditions (unitless); N, impeller speed (rpm); D_i, impeller diameter (m); Ro, density of fermentation broth (kg/m^3); and g_c units' conversion factor (unitless).

For turbulent flow of an ungassed Newtonian fluid with water properties through a flat six-bladed Rushton impeller.

N_p, 6.3 (9–11)
g_c, 1 when using SI units (International System of Units).

If the standard fermentor geometry is equipped with multiple impellers then the total power drawn is roughly proportional to the number of impellers (assuming all impellers on the shaft are the same design, see Ref. 6) thus

$$P_t = P_o \times I$$

where P_t, total power drawn by the fermentor; I, number of impellers on the impeller shaft.

Adding gas (i.e., air) to the fermentor creates gas holdup and decreases the power required. This decrease in power required is calculated using the Michel and Miller equation (14) as follows:

$$\mathrm{Pg} = C\left(\frac{P_t^2 N D_i^3}{Q^{0.56}}\right)^{0.45}$$

where Pg, gassed power input (W); C, constant dependent on the exact fermented configuration; P_t, total ungassed power input to the fermentor (W); N, impeller speed (rpm); D_i, impeller diameter (m); Q, gas flow rate (m^3/sec).

For turbulent flow of an ungassed Newtonian fluid with water properties through a flat six-bladed Rushton impeller in a standard fermentor configuration with the units stated above, $C = 0.112$.

Typically the power is reduced by aeration to between 30% to 100% of the ungassed power.

As an example, for a baffled fermentor filled with 10,000 L of fermentation broth, using three 0.75 m diameter six-bladed Rushton impellers rotating at 80 rpm with an air flow rate of 4000 L/min:

$$\frac{P_o = 6.3 \times 80^3 \times 0.75^5 \times 1000}{1 \times 60^3} = 3544\ \mathrm{W}$$

$$\frac{P_t = 3 \times 3544}{1000} = 10.6\ \mathrm{kW}$$

$$P_t/\mathrm{volume} = \frac{10.6}{10} = 1.1\ \mathrm{kW/m^3}$$

$$\mathrm{Pg} = 0.112 \times \left(\frac{10600^2 \times 80 \times 0.75^3/(4/60)^{0.56}}{1000}\right)^{0.45} = 4.5\ \mathrm{kW}$$

$$\mathrm{Pg}/\mathrm{volume} = \frac{4.5}{10} = 0.45\ \mathrm{kW/m^3}$$

Another important calculation when designing a fermentor is the heat production of the microorganism. This determines the amount of heat that needs to be removed from the fermentor to maintain temperature constant. While this amount of heat is easily removed in small fermentors, when the fermentor becomes very large (>100 m^3), then heat removal capability may become a significant issue, which may necessitate large internal cooling coils or broth being pumped through external heat transfer devices. The heat produced by the microorganisms is proportional to metabolic activity, and the heat production

TABLE 7 The Effect of Scaling Up from a 75-L Tank to a 9500-L Tank, Based on Keeping a Specified Variable Constant

Variable	Constant Reynolds number	Constant shear	Constant power/ unit volume	Constant impeller speed
Power/unit volume	0.0016	0.2	1	25
Impeller speed	0.04	0.2	0.34	1
Impeller diameter	5	5	5	5
Shear	0.2	1	1.7	5
Reynolds number	1	5	8.5	25

Source: Data shown are the ratio of the variable at 9500 L to that at 7% L with one variable kept constant as the basis of scale-up.

has been correlated in aerobic fermentations with the oxygen uptake rate (OUR) by Cooney et al. (15) as follows:

$$H = 0.51 \times \mathrm{OUR}$$

where H, heat evolution (kJ/L.hr); OUR, oxygen uptake rate (mmol oxygen/L.hr).

Scaling up fermentation is not straightforward, as when the volume is changed it is impossible to keep all the variables the same. Table 7 gives an example of what happens when the volume is changed.

What Table 7 demonstrates is that no matter which variable is used as the basis of scale-up (i.e., kept constant upon scale-up), a lot of other important variables change. Thus the challenge of scale-up is to decide which variable is controlling product formation and to ensure that this variable is within the required range upon scale-up. Some of the more commonly used variables for scale-up are

- impeller tip speed,
- oxygen transfer rate (OTR),
- power per unit volume, and
- fluid flow characteristic (e.g., mixing time).

Many more different scale-up criteria are summarized in Kennedy (16,17), including Reynolds number, impeller torque per unit volume, bubble residence time, fluid circulation time, impeller pumping capacity, mass transfer coefficient, etc. The actual industrial plant configuration may not be geometrically similar to the small scale from which data were obtained. This may complicate scale-up calculations. As a rule of thumb, impeller tip speeds of 0.5 to 2.5 m/sec are a useful first approximation for scale-up.

A stirred tank configuration is the most widely used, but not the only configuration for fermentor design. Many other configurations are possible to meet a variety of different fermentation conditions. The most common alternatives to the stirred tank are the bubble column fermentor and the airlift fermentor. These may be used because the microorganism is very shear sensitive and to achieve simplicity of design or reduce costs. Kennedy (18,19) includes a review of fermentor configurations. Continuous fermentation where nutrient is added at the same time as the product is removed is another option. This reduces the fermentor size for a given production rate. Continuous fermentation is applied on the large scale in alcohol production, with New Zealand being the first country in the world to patent and use continuous fermentation for large-scale beer production (18,19). Arguably, the world's largest and most economically important fermentation occurs in continuous plug flow reactors in the rumen of pastoral animals.

In animal cell culture, shear sensitivity can be a significant issue. Cell damage can result from shear forces associated with agitation and also by bubble breakage on gas disengagement. One useful concept in animal cell culture is the Kolmogorov length scale, named after Russian mathematician Andrey Kolmogorov. The Kolmogorov length scale allows the size of the smallest turbulent eddy, which has the most energy dissipation and hence does the most damage to cells, to be estimated. For more discussions on the Kolmogorov length scale, see Kolmogorov (20), Tennekes and Lumley (21), and Croughan et al. (22). General discussions of fermentor design, fermentation monitoring, and optimization of performance can be found in *The Encyclopedia of Bioprocess Technology* (23), *Fermentor Design* (24), *Fermentor Monitoring, Design, and Optimization* (25), and *Fermentation and Enzyme Technology* (6).

V. REGULATION OF MICROBIAL METABOLISM AND PRODUCT FORMATION

Product formation can be affected by the environment outside of the cell, for example, by temperature, pH, dissolved carbon dioxide levels, medium component concentrations, or the OTR. An additional level of control of product formation occurs within the cell where microbial metabolism is very tightly controlled by the action of enzymes within metabolic pathways. This control of enzymes, some of which may influence product biosynthesis, occurs either by influencing the amount of enzyme formed or by changing the activity of the enzymes involved. Table 8 gives a summary of the description of both positive and negative control of enzymes within a cell.

Medium-design experiments are conducted to identify which chemical species control product formation and in which manner. Strategies can be developed to take advantage of product regulation to facilitate production of metabolites. General references to these techniques are developed in Demain (26) and in *The Encyclopedia of Bioprocess Technology* (23). Well-known examples are glucose repression and phosphate repression of enzyme formation. Depending on the nature of the control, various options are available to enhance product synthesis.

A. Strategies to Induce Enzymes Needed for Product Formation

Enzymes needed for product formation may require induction of their synthesis before biosynthesis of the product can attain its full rate. The simplest solution to

TABLE 8 Summary of the Types of Enzyme Control Within Cells

	Positive effect	Negative effect
Enzyme formation	Induction (derepression)	Repression
Enzyme activity	Activation	Inhibition

TABLE 9 Alternatives to Repressible Nutrient Sources

	Repressor	Nonrepressor
C source	Glucose	Glycerol
N source	NH_4	Proline

achieve full induction is to add the chemical that controls enzyme synthesis, the inducer, to the medium (in some cases this inducer may be temperature). If the inducer is not well tolerated by the microbe, then a precursor of the inducer may be more beneficial (27). Alternatively a chemical analog of the known inducer may be a more potent inducer of product formation (28), and so these can be substituted. Perhaps the most convenient solution is to mutate the producing organism and select a strain that is a constitutive mutant that has had the induction control removed, allowing the microorganism to produce all the needed enzymes all of the time (29,30).

B. Strategies to Overcome Nutrient Repression of Synthesis of the Enzymes Needed for Product Formation

Nutrient repression is the negative effect of high concentrations of a given carbon, nitrogen, phosphorus, sulfur, or other nutrient source on product formation. The simplest solution to this problem is to avoid using nutrients in the medium that are known to cause repression. Table 9 shows alternatives to common repressing carbon and nitrogen sources. Another option to avoid repression of biosynthetic enzymes is to keep the concentration of the repressor low throughout the fermentation. Continuous fermentation provides nutrients to the organism at low concentration, often avoiding repression, while supplying enough nutrients to support growth of the organism. Fed-batch fermentation is often used to decouple growth of the organism from product formation by feeding key nutrients for biosynthesis after completion of a growth phase. Feeding nutrients for product formation allows control of the concentration of nutrients at levels below the threshold for repression. Slowly metabolized nutrient sources may release a repressor so slowly that its concentration does not rise above the threshold for repression. An example of slow release is the use of polysaccharides (e.g., starch or sucrose) to slowly release glucose, a classical repressor (31). A genetic solution would be to isolate a repression-resistant mutant (32).

C. Strategies to Overcome end Product Repression

End-product repression occurs when the concentration of a product shuts down its own or another product's formation. One strategy to extend production beyond the threshold end-product repression is to remove the repressive product from the fermentation as it is formed. Ways of doing this might be to add a chromatography resin to the fermentation to absorb the product or to precipitate the product or to circulate the broth through an external extraction system that removes the product with the extracted broth added back into the fermentor. Genetic approaches include selecting a strain that is resistant to a toxic analog of the end product. Where a coproduct is responsible for the repression, this coproduct may be kept at low concentration by using an auxotrophic mutant (a strain unable to synthesize a compound essential for growth) or growing a bradytrope (a slow growing strain that lacks a compound essential for growth, also called a leaky auxotroph) on minimal medium. The auxotrophic mutant and bradytroph strategies are designed to keep the repressible coproduct concentration low to maximize the production of the desired product.

The regulation of metabolite biosynthesis and expression of recombinant vectors are central to any system for the biological production of active pharmaceutical ingredients (API). The building of processes for their manufacture begins with these concepts, their measurement, and their control. More advance reading will provide a guide to details in this domain. Metabolic regulation is described by Greasham and Inamine (29) and by Britz and Demain (32).

Regulation of metabolism, process design for manufacture, and scale-up to commercial production are covered by Flickinger and Drew (23).

VI. GROWTH MEDIA

The primary function of a microbial culture medium is to provide the required nutrients in appropriate forms and concentrations to ensure optimal growth and production of the desired microbial metabolite. The task of developing such a medium can be very challenging, considering the huge diversity of microorganisms and the wide range of nutrients available for designing it. In addition to considering the nutritional value of a medium ingredient, other characteristics must be considered, including cost-effectiveness, consistency, stability, and availability, as well as the potential effect on downstream processing. Fortunately media designed to support the production of a secondary metabolite early in the drug development program may be improved later, since small-molecular products can be well characterized. However, characterization of a biologic is more difficult, requiring the medium formulation to be locked in earlier in the development program. Many different medium-design strategies are available, from simple "one at a time" experiments, experimental designs (e.g., partial factorial designs or Placket and Burman designs), optimization tools (e.g., polynomial fitting) to the use of various artificial intelligence tools (e.g., neural networks). A summary of the strategies available is given in Kennedy and Krouse (33).

The nutritional requirements of most microorganisms are very similar to other biological systems and include sources of carbon, nitrogen, oxygen, hydrogen, and inorganic elements such as sulfur, phosphorus, potassium, magnesium, manganese, calcium, iron, cobalt, copper, zinc, and molybdenum. The relative concentration of these medium components is exemplified in Table 10, a medium for growing the filamentous bacterium *Streptomyces* (34).

Additional nutrients such as amino acids and vitamins—referred to as growth factors—are required if the microorganism is unable to synthesize them. On the basis of the nutrients used, there are basically two types of media, complex and chemically defined. Complex media contain one or more ingredients that cannot be easily defined, such as soybean meal, autolyzed yeast, and corn hydrolysates. As indicated, a chemically defined medium is one in which the chemical composition and quantity of the organic and inorganic components are defined, as shown in Table 10. The initial strategy for developing a cultivation/fermentation medium is greatly influenced by several factors, including how much is known about the cultivation of the desired microorganism or one

TABLE 10 Chemically Defined Medium for Cultivating *Streptomyces griseofuscus*

Medium component	mL/L	g/L
Glucose		112.5
$(NH_4)_2SO_4$		16.5
K_2HPO_4		1.5
Monosodium glutamate		7.5
$CaCl_2$		1.0
Salt solution	20	
P-2000	2	
Salt solution stock		
$MgSO_4{\cdot}7H_2O$		28.9
$ZnSO_4{\cdot}7H_2O$		0.5
$CuSO_4{\cdot}5H_2O$		0.05
$FeSO_4{\cdot}7H_2O$		0.5
$MnSO_4{\cdot}H_2O$		0.1
$CoCl_2{\cdot}6H_2O$		0.04

that is very similar, timeline for medium development, required consistency of the process, and complexity of product isolation (35–37).

In general, media are formulated initially with complex ingredients, ensuring that not only the basic nutrients but also any unknown growth factors are present. Complex ingredients are attractive not only for their nutritional value but also for their relative low cost. Also, since many of these complex ingredients contain "molecular building blocks" for cellular growth, such as amino acids and vitamins, complex media tend to support faster microbial growth compared with chemically defined media, in which the microorganisms must synthesize all of their molecular components. Since complex ingredients are ill defined, consistency is determined by measuring a key constituent or subjecting the ingredient to a "use test" that is usually performed in shake flasks and measures cell growth performance. As product development proceeds so does medium optimization with objectives that may include reducing the complex nature of the medium and increasing consistency, supporting higher productivities, reducing cost, and enhancing downstream processing (29,33). Today, most commercial fermentation processes use complex media. An example of a complex medium to produce the secondary metabolite avermectin consists of the following ingredients (% by volume): cerelose 4.5, peptonized milk 2.4, autolyzed yeast 0.25, and polyglycol P2000 0.25.

Chemically defined media have become popular in recent years and have become the media of choice, especially for the production of biologics, where consistency of the process is very important and efficient isolation of the protein product from the fermentation broth is critical. These media also provide better control and monitoring of the fermentation process, provide rapid scale-up, and reduce sensitivity to large-scale medium sterilization conditions. To achieve optimal performance of the chemically defined medium, nutrient feeding is usually required. Recently, chemically defined media are proving to be commercially beneficial for producing secondary metabolites, for example, penicillin. As an example of actual performance, when the chemically defined medium shown in Table 10 was compared with an optimized complex medium, the chemically defined medium cost 4.5-fold less and increased the physostigmine titer by 80% at the 800 L scale (34).

VII. MEDIUM COMPONENTS

A. Carbon

Usually the most expensive medium component is the carbon source. Several sources of commercial interest are listed in Table 11.

Chemically reduced carbon compounds are utilized to produce cell mass and metabolites as well as provide for an energy source. Although growth on reduced carbon compounds is an exothermic reaction, microorganisms cultivated at laboratory scale usually lose more heat than they generate; however, as cultivation approaches a larger scale in fermentors, just the converse is true. Fermentors must have the cooling capacity to handle high heat loads, especially from high–cell density fermentations. Care must be exercised when adding glucose initially to the medium, since too high a concentration can have a detrimental effect on cell growth. For some bacteria, glucose concentrations greater than 50 g/L will cause dehydration, whereas fungi can tolerate concentrations in excess of 200 g/L. As discussed previously, the level of glucose may also repress enzymes required for the synthesis of secondary metabolites, referred to as catabolite repression (38). One approach at addressing glucose repression is to feed glucose to the bioreactor, maintaining glucose below the repression level. Another approach is to substitute another monosaccharide, polysaccharide, oligosaccharide, or oils for glucose.

B. Nitrogen

A source of nitrogen is required for the biosynthesis of primary nitrogenous metabolites such as amino acids, purines, and pyrimidines, as well as secondary metabolites such as penicillin and tetracyclines. As presented in Table 11, both organic and inorganic nitrogen sources may be used. However, pH drift may be experienced when an organic source, such as amino acids, is utilized by the microorganism as a secondary carbon source, causing deamination and a rise in pH. This rise in pH may be addressed by buffering and redesigning the medium. Like glucose, the concentration of nitrogen may repress the biosynthesis of secondary metabolites (39). Here again, a feeding strategy may be employed to maintain nitrogen at the optimal level.

TABLE 11 Carbon and Nitrogen Sources Used in the Fermentation Industry

Carbon sources	
Cerelose (commercial glucose H_2O)	Soybean oil
Sucrose	Cottonseed oil
Corn syrups, flour	Fructose
Lactose	Black strap molasses
Maltose	Cane molasses
Glycerol	
Nitrogen sources	
Inorganic ammonium salts	Fish hydrolysates
Urea	Amino acids (may also be a carbon source)
Ammonia gas	
Yeast extract or hydrolysates	Sodium nitrate
Flours (cottonseed and soybean)	
Meals (soybean, peanut, fish, rice, barley, and linseed)	

C. Oxygen

In aerobic fermentations, a continuous gaseous oxygen supply is needed to keep this nutrient in sufficient dissolved levels within the fermentation broth. The problem is that the solubility of oxygen in aqueous solution is very low. At 30°C the solubility of oxygen in water is approximately 7.6 ppm (7.6 mg/kg), and oxygen solubility drops with increasing temperature (Fig. 3).

The data on oxygen solubility in water were generated around 1900, and several correlations have been fitted to enable calculation of the solubility as a function of temperature. These are as follows:

$[O_2] = 475/(33.5 + T)$ (8)
$[O_2] = 468/(31.6 + T)$ (43)
$[O_2] = 14.16 - 0.3943.T + 7.714 \times 10^3.T^2 - 6.46 \times 10^{-5}T^3$ (44)

where

$[O_2]$, oxygen concentration in water in contact with air (ppm)
T, water temperature (°C)

All the above correlations work well at fermentation temperatures from 0°C to 50°C (but they do not work well above 50°C). It is important to note that solutes dissolved in water will affect the solubility of oxygen in water. Thus the level of dissolved oxygen in fermentation broth containing sugars and ions may be different to the data for water.

The amount of oxygen in the gas exiting the fermentor is rarely equivalent to that in air (21% oxygen), because oxygen is consumed by the microorganism. The amount of oxygen in the exit gas depends on the amount of metabolizing microorganisms present, how fast the microorganism is growing (and hence the oxygen demand), and the flow rate of gas through the fermentor. Exit gas oxygen composition typically varies between 12% and 21%. Henry's law is particularly useful for calculating the oxygen concentration dissolved in the fermentation broth as a function of the oxygen composition of the gas above the broth (which approximately equals the exit gas composition). The Henry's law

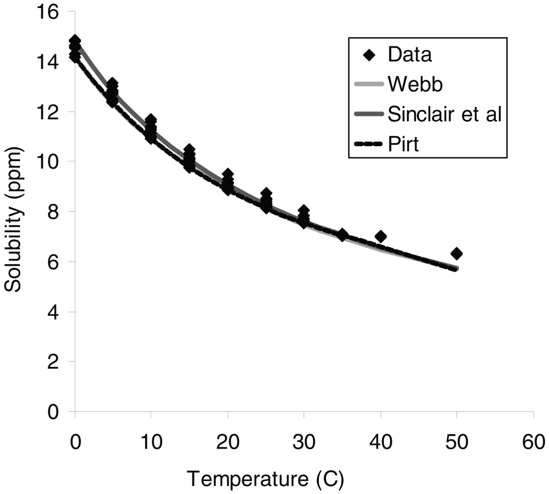


FIGURE 3 The solubility of oxygen in water in contact with air. The fitted lines are the equations generated by various authors, as noted above. *Source*: Data from Refs 40 and 41, fitted curves from Refs 8, 43, 44.

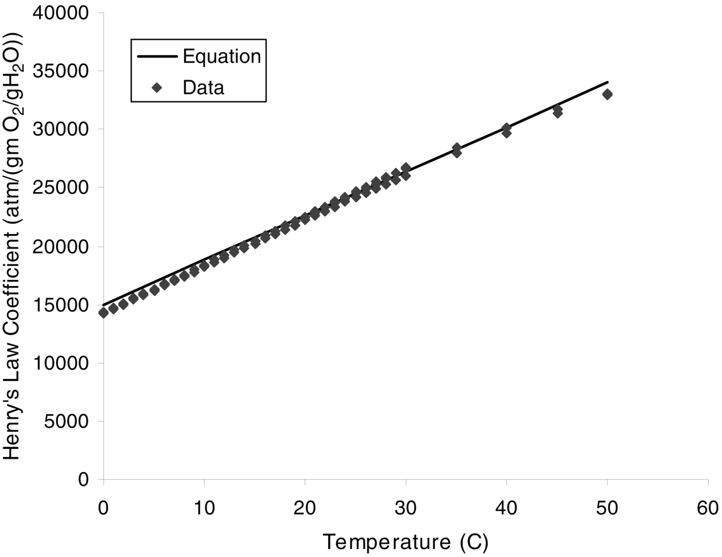


FIGURE 4 Henry's law coefficient for oxygen in water. *Source*: From Refs. 16, 17, and 44.

coefficient is also used in calculating the oxygen mass transfer coefficient online during the fermentation, which is a measure of the mass transfer performance of the fermentor.

Henry's law states

$$[O_2] = \frac{ppO_2}{H} \tag{14.2}$$

where

$[O_2]$, concentration of oxygen dissolved in the liquid phase (g oxygen/g water); ppO_2, partial pressure of oxygen in the gas phase (atm absolute); H, Henry's law coefficient (atm absolute.g water/g oxygen); At 30°C the Henry's law coefficient for oxygen in water is 26,400 atm absolute.g water/g oxygen. This also varies with temperature, as shown in Figure 4, and can be predicted between 0°C to 50°C using the following equation from Kennedy (16,17):

$$H = 7.402 \times 10^3 (2.0259 + 0.05136T) \tag{14.3}$$

where

H, Henry's law coefficient at temperature T (atm absolute.g water/g oxygen)
T, temperature of water (°C)
The Henry's law coefficient levels off above 50°C.

The OTR and carbon dioxide evolution rate (CER) are fundamental parameters that are measured online during the fermentation. Their potential uses include

- an online comparison between fermentation runs available as the fermentation progresses,

- an indicator of when to transfer inoculum into the next fermentation stage,
- a means of calculating the respiratory quotient (RQ)—a useful indicator of microbial metabolic state, for example, to avoid ethanol production in baker's yeast fermentations, and
- a means of calculating online the mass transfer coefficient (k_la) indicative of the oxygen transfer capability of the fermentor.

The main equations programmed into fermentor software controllers or programmable logic controllers (PLCs) are with acknowledgments to the Wang fermentation laboratory (45):

$$\mathrm{OUR} = \left(\frac{Q_{\mathrm{cal}} \cdot P_{\mathrm{cal}}}{V_{\mathrm{L}} \cdot R \cdot (T_{\mathrm{cal}} + 273)}\right) \times \left(\mathrm{O}_{2\mathrm{in}} - \frac{N_{2\mathrm{in}} \cdot O_{2\mathrm{out}}}{N_{2\mathrm{out}}}\right) \tag{14.4}$$

$$\mathrm{CER} = \left(\frac{Q_{\mathrm{cal}} \cdot P_{\mathrm{cal}}}{V_{\mathrm{L}} \cdot R \cdot (T_{\mathrm{cal}} + 273)}\right) \times \left(\frac{\mathrm{N}_{2\mathrm{in}} \cdot \mathrm{CO}_{2\mathrm{out}}}{\mathrm{N}_{2\mathrm{out}}}\right) - \mathrm{CO}_{2\mathrm{in}} \tag{14.5}$$

$$\mathrm{N}_{2\mathrm{out}} = 100 - \mathrm{CO}_{2\mathrm{out}} - \mathrm{O}_{2\mathrm{out}} \tag{14.6}$$

$$\mathrm{RQ} = \frac{\mathrm{CER}}{\mathrm{OUR}} \tag{14.7}$$

$$\mathrm{k_la} = \frac{\mathrm{H} \cdot \mathrm{OUR}}{\mathrm{ppO}_2^* - \mathrm{ppO}_{2\mathrm{L}}} \tag{14.8}$$

$$\mathrm{ppO}_2^* = \mathrm{O}_{2\mathrm{out}} \cdot P_{\mathrm{f}} \tag{14.9}$$

$$\mathrm{ppO}_{2_{\mathrm{L}}} = \mathrm{DO} \cdot P_{\mathrm{f}} \tag{14.10}$$

where

CER, carbon dioxide evolution rate (mmol carbon dioxide/L unaerated fermentation broth per hr)

CO_{2in}, carbon dioxide composition of the fermentor inlet gas (vol%), usually 0.03%

CO_{2out}, carbon dioxide composition of the fermentor outlet gas (vol%)

DO, dissolved oxygen measurement (% of saturation at 1 atm), measured by DO probe

H, Henry's law coefficient at the temperature of the fermentation broth (atm absolute.g broth/g oxygen), usually assumed to be that of oxygen in water

K_la, oxygen mass transfer coefficient (hour^{-1})

N_{2in}, total inert gas composition of the fermentor inlet gas (vol%), usually taken as the N_2 + Argon = 78.1 + 0.9 = 79%; referred to as N_{2in} as most of the inert gas is nitrogen

N_{2out}, inert gas composition of the fermentor outlet gas (vol%); referred to as N_{2out} as most of the inert gas is nitrogen

O_{2in}, oxygen composition of the fermentor inlet gas (vol%), usually 20.9%

O_{2out}, oxygen composition of the fermentor outlet gas (vol%)

OUR, oxygen uptake rate (mmol oxygen/L unaerated fermentation broth per hr)

TABLE 12 Volumetric Composition of Air

Major constituent	Composition (vol%)
Nitrogen	78.08
Oxygen	20.95
Argon	0.93
Carbon dioxide	0.03

Source: From Ref. 46.

P_{cal}, pressure of calibration of inlet gas mass flow meter, usually 1 atm absolute
P_f, total pressure above the fermentation broth (atm absolute)
$ppO_2{}^*$, partial pressure of oxygen in the gas above the fermentation broth (atm absolute)
ppO_{2L}, partial pressure of oxygen in the fermentation broth (atm absolute)
Q_{cal}, gas flow rate into the fermentor as measured by a mass flow meter calibrated under standard conditions, usually calibrated via wet test meter at 25°C and 1 atm absolute
R, universal gas constant, 8.3146 J/mol.K
RQ, mmol carbon dioxide/mmol oxygen, often shown as a unitless ratio.
T_{cal}, temperature of calibration of inlet gas mass flow meter, usually 25°C
V_L, unaerated liquid volume in the fermentor (L)
The composition of air is shown in Table 12.

If the inlet gas mass flow controller is calibrated at 25°C and 1 atm absolute, for example, via wet test meter, then

$$\mathrm{OUR} = \left(\frac{24.54 \cdot Q_{cal}}{V_L}\right)\left(\mathrm{O}_{2\mathrm{in}} - \left(\mathrm{O}_{2\mathrm{out}}\left(\frac{79}{100 - \mathrm{O}_{2\mathrm{out}} - \mathrm{CO}_{2\mathrm{out}}}\right)\right)\right) \tag{14.11}$$

$$\mathrm{CER} = \left(\frac{24.54 \cdot Q_{cal}}{V_L}\right) \times \left(\left(\left(\frac{79}{100 - \mathrm{O}_{2\mathrm{out}} - \mathrm{CO}_{2\mathrm{out}}}\right) \times \mathrm{CO}_{2\mathrm{out}}\right) - \mathrm{CO}_{2\mathrm{in}}\right) \tag{14.12}$$

Here Q_{cal}, the gas flow rate into the fermentor, is in L/min, V_L is the unaerated fermentation broth volume in L, gas compositions are in vol%, and CER and OUR are in mmol/L.hr.

An example calculation for a benchtop fermentor where the inlet mass flow meter was calibrated at 25°C and 1 atm absolute pressure.

A fermentor with a unaerated volume of 4.37 L has an air flow of 4.8 L/min entering it.

Inlet CO_2 = 0.05%
Inlet O_2 = 20.9%
Outlet CO_2 = 1.35%
Outlet O_2 = 19.5%
Fermentor pressure = 1.1 atm absolute
The measured dissolved oxygen is 30% of saturation.

Then

$$\mathrm{OUR} = \frac{24.54 \cdot 4.8}{4.37}\left(20.9 - \left(19.5\left(\frac{79}{100 - 19.5 - 1.35}\right)\right)\right) \tag{14.13}$$

$$= 38.7\ \mathrm{mmoles/L.hr}$$

$$\mathrm{CER} = \frac{24.54 \cdot 4.8}{4.37}\left(\left(\left(\frac{79}{100 - 19.5 - 1.35}\right).1.35\right) - 0.05\right) \tag{14.14}$$

$$= 35.0\ \mathrm{mmoles/L.hr}$$

$$\mathrm{RQ} = \frac{35.0}{38.7} = 0.90\ \mathrm{mmoles\ CO_2.mmoles\ O_2^{-1}} \tag{14.15}$$

$$\mathrm{ppO}_2^* = \frac{19.5}{100} \times 1.1 = 0.214\ \mathrm{atm\ abs} \tag{14.16}$$

$$\mathrm{ppO}_{2\mathrm{L}} = \frac{20}{100} \times 0.21 \times 1.1 = 0.046\ \mathrm{atm\ abs} \tag{14.17}$$

$H = 7.402 \times 10^3 (2.0259 + 0.05136 \times 35) = 28302$ atm absolute.g broth/g oxygen

$$k_{\mathrm{L}}a = \frac{28302 \times 32}{10^6} \times \frac{38.7}{(0.214 - 0.046)} = 208.4/\mathrm{hr} \tag{14.18}$$

These online calculations, besides being useful for monitoring the fermentation and comparing it to previous batches, can also be used in process control of the fermentation. For example, the CER can be integrated (totaled over time) and the total amount of carbon dioxide evolved correlated with the amount of carbon source consumed. A typical value for this correlation for *Bacillus subtilis* growing on glucose as the carbon source and fishmeal as the nitrogen source is 16.9 mmol carbon dioxide per gram of glucose consumed. This carbon dioxide yield on substrate will vary depending on the microorganism and the medium composition. *B. subtilis* growing on glucose as the carbon source and nutrient broth as the nitrogen source gives 11.3 mmol carbon dioxide per gram of glucose. Thus the coefficient must be generated for each individual system. Once the coefficient is known then the CER can be used online to time glucose additions to maintain the glucose concentration constant throughout the fermentation. Further if the yield of cells on glucose is known (a typical figure is 0.5 g cell per g glucose consumed), then the cell mass concentration can also be estimated online. Such a process control scheme is accurate during cell growth. Typically during the end of the fermentation when growth is low or when repression is operating or when product formation is significant, then the coefficients will change. A further refinement might be to program the coefficient changes as a function of the estimated growth rate.

Many other fermentation process control strategies are possible. The dissolved oxygen signal can be used to control glucose addition by assuming that once the glucose has become limited, then any increase in dissolved oxygen signals that growth is slowing down. Addition of more glucose linked to a minimum dissolved oxygen threshold will continue growth at the rate of addition of the critical nutrient. Feeding schemes based on pH or other signals are also possible.

Control of dissolved oxygen to a minimum level in the fermentation broth is very important to avoid metabolic limitations. There are four ways of increasing the dissolved oxygen concentration:

- Increase the impeller speed.
- Increase the air flow rate into the fermentor.
- Increase the pressure of the fermentor.
- Decrease the microorganisms growth rate and hence oxygen demand, for example, by changing temperature or pH or reducing carbon feeding.

Each of these strategies comes with disadvantages if taken to extremes. Too high an impeller speed may create too much shear for a shear-sensitive microorganism or draw too much power for the impeller motor. Too high an air flow rate can lead to foaming, resulting in too much antifoam addition or difficulty in containing the broth within the fermentor. Too high an air flow rate can remove important volatile intermediates or lead to air flooding of the zone around the impellers, decreasing their effectiveness. There is usually a limit to the pressure at which the fermentor is certified to safely operate. Increasing fermentor pressure not only increases the oxygen content of the liquid according to Henry's law, but it also correspondingly increases the dissolved carbon dioxide concentration in the fermentation broth. High levels of dissolved carbon dioxide can be inhibitory to some microorganisms. Slowing microbial growth extends the fermentation and may interfere with product formation. When fermentation has a high oxygen demand, a combination of these strategies is used to optimize performance.

Within appropriate limits specified for each strategy, it is usual to sequentially exhaust the effects of one strategy and then move on to the next. This raises the interesting question as to which order to implement the strategies, for example, impeller speed, then air flow rate, then pressure, then growth rate, or in some other order. The order chosen may be specific to the fermentation in question; for example, increased impeller speed would not be tried first for shear-sensitive microorganisms, and increasing air flow rate would not be tried first for a medium with a propensity to foam. The air flow rate into the fermentor is usually controlled by the air inlet mass flow controller, and the pressure in the fermentor is controlled by the air outlet mass flow controller. It is important to note that during control strategies, these two controllers can interact detrimentally with each other, as the air flow rate affects pressure in the fermentor. It is thus possible for these two controllers to "fight" each other if they are both controlled by the usual proportional, integral, derivative (PID) controllers simultaneously. Decoupling these interactions is difficult; therefore the best strategy is to control these controllers sequentially by having one manually set rather than operate both via control algorithms together. A last-ditch attempt to increase oxygen content of the fermentation broth may be to enrich the oxygen content of the inlet air. This may have significant negative consequences for process economics as well as pose a safety hazard. For these reasons it is rarely used as a strategy on the industrial scale.

D. Inorganic Elements

The inorganic elements stated earlier are important in intermediary metabolism, constituents of phospholipids, nucleic acids, amino acids, and some secondary metabolites. The trace elements (magnesium, zinc, copper, iron, magnesium, and cobalt) are important as cofactors or activators of enzymes and regulators of secondary metabolism. These are frequently added to the medium as "contaminants" of other medium ingredients, including water.

E. Inducers

Media may also contain compounds that are required to induce the biosynthesis of a desired product. For example, isopropylthio-β-D-galactoside may be added to an *Escherichia coli* fermentation medium to induce production of the recombinant protein. D-Xylose is required for producing D-glucose isomerase in *Streptomyces* (47).

VIII. MEDIUM STERILIZATION

Sterilization of the medium is a crucial part of the fermentation process. It is a balance between applying enough heat energy to kill unwanted microorganisms to form a sterile medium and avoiding destroying important nutrients in the same process. The equation governing the sterilization process is an Arrhenius-type law as follows:

$$\Delta = \mathrm{Ln}\left(\frac{N_\mathrm{o}}{N}\right) = \int A \exp\left(-\frac{E_\mathrm{a}}{RT}\right) dt \tag{14.19}$$

where Δ, Del factor or Rho, a dimensionless numerical measure of heat impact (6); N_o, presterilization microbial or nutrient count (number or concentration); N, poststerilization microbial or nutrient count (number of concentration); A, Arrhenius constant (s^{-1}); E_a, activation energy of microbial death or nutrient destruction (J/mol); R, universal gas constant (J/mol.K); T, temperature (K).

The above equation is calculated during the heating, holding, and cooling phases of a sterilization run, with typically the heating portion being 20% of the total heat load applied, the holding period being 75% of the total heat load applied, and cooling being 5% of the total heat load applied (6). Most of the heat impact is in the holding period.

This equation has several important implications. The microbial killing power is exponentially related to temperature. Thus sterilization times decrease considerably with increasing temperature. As this is such a steep curve, getting temperatures correct and evenly distributed during sterilization is very important. At 121°C the time for sterilization will be 15 to 30 minutes, whereas at higher temperatures it may be seconds. This opens the opportunity for high temperature–low time continuous sterilization procedures if a nutrient is very temperature sensitive. The Del factor or Rho is a very useful calculation to compare the heat energy impact of sterilization on scale-up or between commercial runs.

The temperature of saturated steam inside the fermentor during sterilization is set by the fermentor pressure. The correlation between steam temperature and fermentor pressure is shown in Table 13. It is very important to

TABLE 13 Temperature and Pressure of Saturated Water and Steam

Temperature (°C)	Pressure (bar absolute)
100	1.013
105	1.208
110	1.433
115	1.691
120	1.985
121.8	2.100
125	2.321

Source: From Ref. 48.

TABLE 14 Sterilization Activation Energies of Some Nutrients and Microbial Strains

Entity	Activation energy, E_a (kJ/mol)
Folic acid	70.2
Riboflavin	85.7
Hydrolysis of casein	86.1
α-Panthothenyl alcohol	87.8
Thiamine HCl	92.0
Cyanocobalamin	96.6
Bacillus stearothermophilus	283.0
Putrefactive anaerobe NCA 3679	302.6
Bacillus subtilis	317.7
Clostridium botulinum	342.8

Source: From Refs. 6 and 49.

remove all air from the fermentor by running the fermentor in free-steaming mode prior to the holding temperature. Air in the fermentor can be detected by observing the temperature and pressure measurement made inside the fermentor. If air is present the temperature and pressure will not match the steam table values in Table 13.

A key to avoiding contamination during sterilization is to carefully control the pressure of the fermentor during cooling of the fermentation broth after sterilization. If the cooling rate is very fast, the steam inside the fermentor may collapse quickly, leading to a vacuum. A vacuum can let in contaminants through any joints not 100% sealed. To avoid this vacuum becoming established, it is usual to start air sparging through the fermentor as the temperature approaches 100°C during the cooling cycle.

The ability of sterilization to kill microbes and leave nutrients relatively unaffected is related to the difference in their activation energies (Table 14). The activation energy of microbial destruction is an order of magnitude greater than that of destruction of the nutrients listed, which enables killing of microbes without completely destroying all nutrients. Typically, in calculations, *Bacillus stearothermophilus* is used as the example microbe, as it is one of the most heat resistant of the microbes (Table 14), and hence it represents a conservative view of the contaminants present in the initial medium. *B. stearothermophilus* can be assumed to have an Arrhenius constant of $10^{36.2}$ s^{-1}. Riboflavin is usually taken as the representative nutrient component. It should be noted that the data in Table 14 pertain to the vegetative state of the microbes and that spores or other resistant structures are very much more difficult to kill with heat. Table 15 presents the relative heat resistance of various morphologies.

TABLE 15 Relative Resistance of Various Microbial Morphologies to Moist Heat

Microbial system	Relative resistance
Vegetative bacteria and yeast	1.0
Bacterial spores	3×10^6
Mold spores	2–10
Virus and bacteriophage	1–5

Source: From Ref. 6.

The amount of decrease in microbial burden of the medium during sterilization is usually presented as log decreases. This raises the question of how many log decreases in microbial count should the sterilization process be designed to deliver. The answer to this depends on the initial contamination levels of the nutrient. This number is highly variable depending on the nature of the nutrient. A dried, purified chemical component may have a count as low as 10^2 g^{-1}, whereas a relatively crude industrial medium component that has not been made under strictly controlled conditions may have a count of 10^8 g^{-1} or even much higher. Another decision is what fractional number of microbes is the acceptable sterility level. A microbial number value after sterilization of 10^{-3} microbes in the fermentor gives a theoretical 1 chance in 1000 that the sterilization will not achieve sterility. Other practitioners may use a more conservative 10^{-6} microbes per fermentor as the definition of sterility. Example calculations of sterilization using the Arrhenius type law can be found in Aiba et al. (13) and Wang et al. (6).

It is important to understand that calculations like the Arrhenius equation above allow the theoretical sterilization time to be calculated, but this time needs to be modified by practicality. If solid substrates are present in the medium, then it will take a lot longer for heat to penetrate to the center of such particles than sterilizing a defined medium. If the fermentor is old or doubts held over certain design aspects, then a more conservative approach to sterilization times may be taken.

It is crucial to understand that sterilization is a statistical process with a probability of failure rather than a guaranteed sterile/not sterile crisp outcome. This has implications on the industrial scale in that a certain contamination rate will be inevitable. Typically a fermentation contamination rate of less than 1 in 20, or 5%, is expected. However, the contamination rate is rarely regular, for example, once every twentieth run. After a run has been contaminated, the source of the contaminant may be unknown and a conservative approach taken. It can take a few attempted runs before a contaminant-free run is obtained, with each failed run leading to ever more conservative practices.

Early signs of a contaminated fermentor may include:

- a different smell in the fermentation room.
- a different set of data readings to that normally expected, particularly a change in pH profile or a rapidly dropping dissolved oxygen concentration, and
- a different morphology of microbe, for example, under the microscope, or increase in viscosity.

The definitive answer is usually found by looking under the microscope or by plating out the microorganism. The identity of the contaminant microorganism can give good clues as to the source of the contaminant. If the contaminant is a waterborne microorganism, then leaks from cooling coils, from water-cooled seals, or other water sources should be investigated. If the microorganism is one normally found in the air, then filters or seals should be investigated. If the microorganism is normally present on skin then human handling errors can be suspected. Checking the sterility (aside from the desired microorganism) of the inoculum is a vital piece of evidence in contamination investigations, as it indicates whether the contaminant came through with the inoculum or not.

Contamination of the fermentor with microbial spores presents one of the most demanding challenges to regain sterilization of the fermentor vessel. Microbial spores are very difficult to inactivate by conventional sterilization strategies, as shown by their relative heat resistance in Table 15. The answer to this is to use a Tyndallization process, named after nineteenth-century scientist John Tyndall (50). In this process, after contamination with spores, the fermentor is heated to sterilization temperatures, which kills the vegetative state of the microorganism and leaves the spores still present and viable. The fermentor is then filled with rich nutrients and incubated, causing the spores to germinate into the vegetative state. These newly vegetative microorganisms can then be killed by conducting a second sterilization. Several cycles of rich nutrients, followed by sterilization, can be used to remove all of the spores. An extremely thorough fermentor disassembly and cleaning may also be required.

IX. GROWTH KINETICS

As expected, the unicellular and filamentous microorganisms exhibit different growth characteristics. Each unicellular microorganism grows to a certain size and divides to produce two complete cells. These two cells grow and divide at approximately the same rate as the parent cell. Thus, during active cell growth, these microorganisms exhibit logarithmic or exponential growth and exhibit a growth rate that is expressed in terms of the generation time of the culture. Although yeast is also unicellular, it multiplies by budding, exhibiting linear growth. Usually both of these microbial types demonstrate dispersed growth in liquid media; however, they may aggregate if the growth medium or other environmental parameters are changed.

The cellular growth of the filamentous bacteria (such as the industrially important actinomycetes) and fungi is by formation and extension of filaments (hyphae), resulting in lateral and apical branches. When cultivated in liquid media, these filamentous microorganisms can exhibit different morphological types, ranging from dispersed filamentous growth to loosely or tightly packed hyphae balls referred to as pellets. When the culture is present as dispersed filaments, growth is reported to be exponential (2) as well as linear (51). However, when present in the pellet form, growth is considered to be in a linear relationship between the cube root of the biomass concentration and cultivation time. The rather high broth viscosity that may be associated with dispersed filamentous growth can be problematic, increasing the cost and efficiency of mixing. By changing the chemical and physical fermentation parameters, small-pelleted growth may be achieved, greatly reducing the viscosity of the fermentation broth and decreasing the cost of mixing.

When a bioreactor containing a growth medium is inoculated with a small number of microbial cells, three phases of cellular growth are observed, as

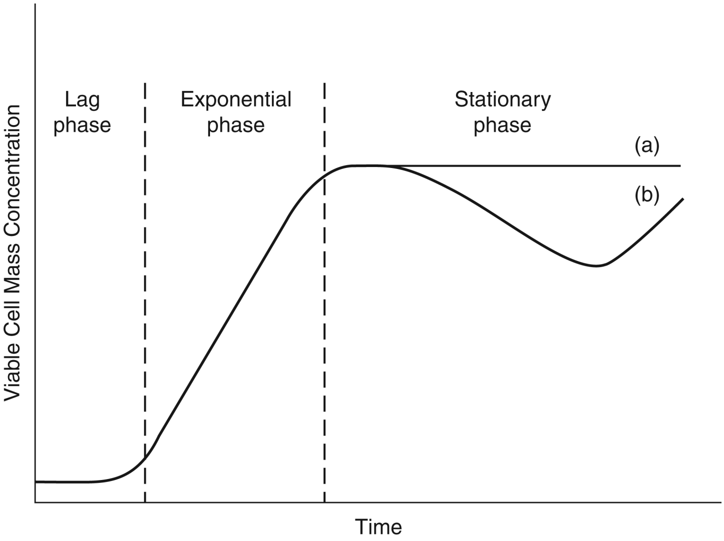


FIGURE 5 Fermentation kinetics.

shown in Figure 5. In the lag phase, cells are adapting their metabolism for utilization of the nutrients in the growth medium. If inoculum levels were low they may also be actively growing but at levels below the minimum detectable level of the cell concentration assay. Cells in the exponential phase are growing rapidly, since no nutrient is limiting and there is no build-up of growth inhibitory metabolites. When the cells begin to experience nutrient limitation and/or inhibitory metabolites, a cessation of active growth is observed, marking the initiation of the stationary phase of growth. If cell growth equals cell death, the culture will maintain a constant viable cell mass (curve a). As expected, an increase in cell death yields a decrease in viable cell mass Figure 5 (curve b). However, the cells regrow at the end by utilizing the nutrients from cells lysed during the preceding death phase.

During rapid growth, cellular functions are supported by primary metabolism. When discussing the production of a secondary metabolite, this phase of growth is referred to as the trophophase, as illustrated in Figure 6 for the production of avermectin, an anthelmintic (52). As shown, the biosynthesis of avermectin begins as the cells switch from primary to secondary metabolism. This latter phase is referred to as the idiophase.

X. SEED TRAIN

A typical seed train (Fig. 1) may be initiated by thawing a frozen vial from the working cell bank and aseptically adding the contents to a 250-L shake flask containing 50 mL of a medium designed to support rapid growth. The flask is incubated on a shaking platform at a specific temperature. Once the culture reaches late exponential or linear growth, aliquots are removed and used to inoculate 2-L shake flasks, each containing about 500 mL of the same growth medium and incubated as described above. Again, after the culture reaches late

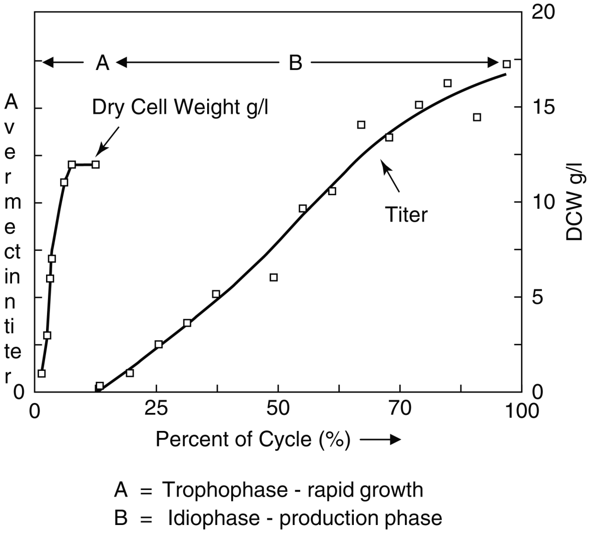


FIGURE 6 *Streptomyces avermitilis* growth and avermectin formation.

exponential or linear growth, the contents of the 2-L flasks are aseptically pooled and used to inoculate the 280-L seed fermentor containing approximately 180 L of the same growth medium. This fermentor will usually be capable of supplying exhaust gas samples for online determinations of the OUR and CER. When the culture reaches the end of active growth, as measured by exhaust gas analysis, it is transferred to the production fermentor. Alternatively some cultures may benefit from transfer in midlog phase, also indicated by exhaust gas analysis. Here, the medium may be the same as that used in developing the inoculum or one that has been designed specifically for supporting optimal product production. Though well-behaved inoculum development may lead to predictable times of culture transfer, it is generally better to trigger the culture transfers on the basis of measured parameters. This approach maintains control over performance and reduces the potential for process drift. Many seed trains use off-line measurements for culture transfer criteria at the shake-flask scale, such as cell mass, nutrient completion, and pH. Seed trains that are similar to the one just described are commonly used today with both complex and defined media.

XI. REDUCING VARIABILITY AND THROUGHPUT TIME IN INOCULUM DEVELOPMENT

Variability in inoculum performance results from three primary sources: (*i*) contamination during transfer from one stage to the next, (*ii*) long inoculum development cycles that amplify intrinsic biological variability, leading to inocula at variable states of physiologic readiness, and (*iii*) uncontrolled variability in components of complex media. Because typical seed trains have a number of manual operations at the shake-flask scale, the chance for contamination increases as a function of the number of transfers from one stage to the next. To address this potential issue, fermentation processes are beginning to emerge that reduce the number of transfers leading to commercial-scale

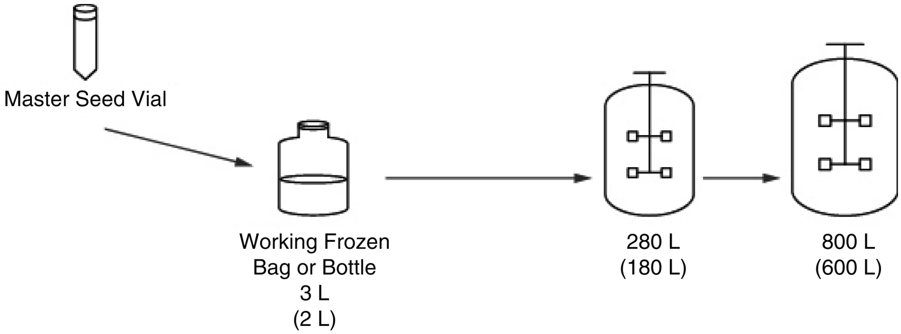


FIGURE 7 Optimized inoculum development.

production. Instead of preparing frozen vials of the working cell bank from a shake-flask culture, 2 to 3-L frozen bags of the working cell bank are prepared from a culture in the late exponential or linear growth phase, cultivated in a small pilot plant fermentor (1). This approach allows preparation of the working seed cultures at the same optimal physiological state. By using the frozen bags versus the vials, the shake-flask stages of inoculum development are eliminated (Figure 7). The thawed content of the working cell bank bag is transferred to a seed fermentor or directly to the production fermentor, employing a "closed" system that minimizes contamination. This approach also results in a shorter inoculum development time period and, if a seed fermentor is used, allows culture transfers based on online respiration profiles. Further reduction in variability will result from development of defined media for inoculum development.

XII. DOWNSTREAM PROCESSING

The separation strategy used to isolate the product from the fermentation broth and then purify it to the final product is very specific to the chemical nature of the molecule to be separated, the purity of the product required, the yield of product expected, and the nature of the fermentation broth. The downstream processing protocol is often worked out on a case-by-case basis. Often fermentation medium design and the conditions used during fermentation have a big impact on downstream processing. For example the use of antifoam in the fermentation to control excessive foaming can make downstream processing more difficult. A fermentation medium containing lots of protein, for example hydrolysates, may require additional steps to fully recover a protein product. Properties of the fermentation broth may change physical properties of the harvest broth, leading to unusually high viscosities or to emulsions in downstream processing.

The primary determinant in establishing a downstream processing protocol is the chemical nature of the product. If the product is a small molecule or a lipid, then solvent processing may be required to separate the product from the aqueous broth. Examples of industrially relevant small molecules include antibiotics, antifungals, immunesuppressors, and cytotoxins. If the product is a protein or a large polypeptide, then aqueous-based processing, such as adsorption on a resin, may be needed to separate the product from the fermentor broth. Examples of industrially relevant proteins include enzymes, vaccines, and monoclonal antibodies. Conventional approaches to isolation and purification of small and large molecules can be found in *The Encyclopedia of Bioprocess Technology* (23) and in *Bioseparations Science and Engineering* (53). Another method of processing, supercritical fluid extraction (and variations upon this technology), is increasing in popularity. Traditionally supercritical fluid technology was applied solely to the separation of nonpolar materials. However, by using cosolvents and other techniques, molecules that are more polar may also be separated (54).

The type of processing (solvent based, aqueous based, or supercritical) has a major impact on facilities and operating strategies. If solvent-based processing is needed then a suitable solvent rated facility is required. This flameproof rating is very expensive due to the need to meet appropriate safety and hazardous goods regulations. If supercritical fluid processing is chosen then pressure vessels, with the attendant safety compliance, are needed. By comparison aqueous-based processing is usually less capital cost intensive.

After the type of processing is set, often the first choice the separation protocol designer has to consider is cell separation. Whether and how to separate cells depends on where the product is located and how efficient the extraction process is. If the product of interest is located nearly 100% within the cells or nearly 100% in the fermentation liquid supernatant, that is an excreted product, then separating the cells from the remainder of the broth can make extraction easier and most importantly the volume of material to process may become much smaller (which has a significant economic advantage). The reality is that for most secondary metabolites involved in solvent processing, the product is rarely distributed uniquely in the cells or the supernatant, but it is usually split between the cells and the supernatant. This split, the product partition coefficient, may be affected by fermentation conditions and so may vary from run to run. The worst-case scenario is when 50% of the product is within the cells and 50% outside the cells in the supernatant.

XIII. SOLVENT PROCESSING

The classic example of solvent extraction to purify small molecules from fermentation broth is the extraction of penicillin, including the use of Podbielniack separators. A useful summary of this classic process can be found in *The History of Penicillin Production* (55).

The first stage in solvent processing is the decision of whether to separate the cells and supernatant or whether to conduct a whole broth extraction upon the unseparated broth. If the product is partitioned into only the cells, then this decreases the volume of solvent needed for extraction of the separated cell paste compared to a whole broth extraction. As a typical solvent extraction volume ratio is 0.3:1.0 (volume of solvent to volume of fermentation broth), then starting with a much more compact cell paste of small volume saves a tremendous amount of solvent and the need for large tanks. If the product is partitioned only into the broth supernatant, then removing the cells may have the advantage of removing emulsion-forming capability or otherwise aid by having a less difficult separation requirement. If the product is partitioned into both the cells and the broth supernatant, then whole broth extraction is the likely most sensible option.

Another method is to combine solvent extraction and centrifugation in one step. The advantages of such an approach include higher extraction yields and quicker extraction times. Separation of cells from broth supernatant is not easy in a solvent environment due to the explosion-/flameproof nature of the separation equipment required. Although such solvent-rated centrifuges are on the market, they are a considerable capital cost, and so smaller facilities may stick with either separating the cells in an aqueous environment prior to extraction or conducting whole-broth extractions. Microfiltration may be used as an alternative to centrifugation for cell removal.

Gravity-based whole-broth extractions are simple but can be susceptible to emulsion formation, take a considerable time for extraction (days), and can have a lower yield. Impeller configuration to avoid emulsion formation is a concern with such systems. Typically the broth is pumped into a solvent tank, and two layers, a broth layer and a solvent layer, will form. Whether the broth is the top or bottom layer will depend on the solvent density. Mixing must then occur to gently disturb the interface between the solvent and the broth to enable mass transfer to occur with the product traveling from the broth into the solvent layer. The challenge is to stir fast enough to get rapid mass transfer but not fast enough to get an emulsion, which can be very difficult to break. The nature of the emulsion and whether it is easy to break determines the vigor of the mixing, which may range from turbulent agitation to very mild laminar flow conditions. It is desirable to have one impeller in the solvent layer and another in the broth layer so that careful control of the interface is maintained. The ultimate configuration is to have these two impellers on different shafts (one top mounted, the other bottom or side mounted) so that independent speed control of the upper and lower impellers is possible. If only gentle agitation is required, then radial flow impellers, which pump liquid to the tank edges, are preferred rather than axial flow impellers, which pump liquid upward into the interface, creating turbulence.

When an unbreakable emulsion forms, the product is lost into the emulsion, which becomes unavailable for further processing. When an emulsion forms, several options can be tried to break it, including turning down (or off) the agitation and letting gravity separate the phases (time consuming and often not that effective), adding salt or other chemical to destabilize the emulsion, or adding more solvent (expensive and increases processing volume). Prevention is much better than cure when it comes to emulsions.

Many variables can affect the speed of whole-broth extraction. Of particular relevance is the viscosity of the fermentation broth. This may vary widely from fermentation to fermentation. In a series of batch processes, the operator in charge of extraction will have to fine-tune the extraction process to the state of the incoming fermentation broth. This adds complexity to the processing and emphasizes the strong interaction between fermentation conditions and separation processes.

One critical decision that needs to be made early on is which solvent to select for the extraction. This is not an easy decision, as numerous variables influence the choice. For example, excellent extractions done on the bench scale using chlorinated solvents may not be scalable due to environmental prohibitions on using chlorinated solvents at the industrial scale. The cost of the solvent may prohibit the use of certain expensive solvents. If solvent is to be recycled, then highly volatile solvents may be avoided due to losses in the recycling process. Another factor affecting solvent choice is acidity, heat, and/or light sensitivity of the product molecule. For example, a product that is acid sensitive precludes the use of ethyl acetate or chloroform (56). Most importantly the solvent should have high preferential solubility for the product of interest and low solubility of coproducts or contaminants. Usually a whole range of different solvent types are tested at laboratory scale to give maximum flexibility to solvent choice.

After extraction the solvent containing the product is removed from the whole broth and the solvent volume is reduced by evaporation. This gives a much smaller volume of solvent to process through further purification steps. A falling film evaporator or similar is usually used.

After a small volume of solvent containing the product of interest is obtained, a series of other separation techniques are used to separate the product from impurities. The nature of these steps is determined by the nature of both the product and the impurities. The more chemically similar the product of interest and the impurities, the more difficult the separation and the more the separation steps needed.

Minimizing the number of separation steps is vital on the industrial scale. This is because each separation step has a given efficiency, meaning the product is lost in each separation step. Table 16 shows the drop in yield of product after a number of steps of separation. The drop in yield as the number of separations increases is very precipitous. For this reason, process intensification (combining processing steps) or using a small number of simple steps is often preferred economically. If the product is too difficult to separate from a closely related coproduct, then the ultimate solution may be to vary the microbial metabolism to avoid making the coproduct (or to increase the product/coproduct ratio) rather than use ever more sophisticated separation steps. Obtaining mutants that do not produce the coproduct, genetically engineering the organism or chemically/enzymically reacting the coproduct away, may be more productive than more separation steps. In reality the yield of some separation steps may drop to 80%, and so in practice it is usual to have no more than five to six separation steps. For a typical secondary metabolite an overall yield of 50% (crystalline product as a % of the product present in the fermentation broth at harvest) is not unusual.

Following solvent extractions the purification protocol will be tailored to the molecule and impurity profile involved. Two common unit operations used in such protocols are chromatography and crystallization. Chromatography steps can be chosen from a wide variety, including silica gel, modified medium

TABLE 16 Influence of the Number of Separation Steps and the Yield of Product Remaining, Assuming a 95% and 90% Yield from Each Individual Separation Step

Number of separation steps in protocol	Yield (%), given each separation step is 95% efficient	Yield (%), given each separation step is 90% efficient
0	100	100
1	95	90
2	90	81
3	86	73
4	81	66
5	77	59
10	60	35
15	46	21

polarity phases like silica-diol, and C-8 (56). One of the challenges of using large-scale chromatography columns is to avoid channeling. Channeling involves a tunnel forming in an incorrectly packed column. This channel allows material distributed onto the top of the column to directly bypass the packing material and exit the column without any separation taking place. As a result prepackaged and validated columns purchased directly from manufacturers have increased in popularity. An important aspect in chromatography is the amount of material loaded onto the column. The amount of material that the column is capable of dealing with is related to the amount of product put onto the column rather than the concentration of the product in the incoming material.

Scale-up of chromatography columns occurs in a different manner than the scale-up of other unit operations. Normally scale-up occurs by scaling based on geometric similarity. Geometric similarity results in height to diameter ratios being maintained. However, when scaling up chromatography the height is not increased, but the diameter is increased, leading to low squat columns. Separation capability is related to the height of the column, and flow rate is related to the diameter of the column; thus only the diameter is increased to process more material.

Crystallization occurs when conditions are manipulated so that the solubility limit of the product in the solvent is exceeded and the product crystallizes out of solution as a solid. This manipulation is usually achieved by changing solvent mixture concentrations or via temperature changes. Crystallization is very temperature sensitive, and in some cases nucleation of crystallization may have to be encouraged by "seeding" the solution with a few product crystals from a previous run. One particular issue for pharmaceutical application is the polymorphic nature of the crystals produced. Some chemicals may exhibit a variety of crystal morphologies. It is important for reproducibility and in some cases biological activity that crystals of one specific morphology be consistently produced. Another issue may be the trapping a liquid within the formed crystal, known as inclusions. Producing the correct crystals still has an art form component.

After crystals are made the excess solvent in the crystals needs to be removed in steps commonly known as drying (even though there is often little water present). This may be achieved by use of a vacuum oven. The final steps are product assay and packaging.

Many variations on this general scheme (solvent extraction, then chromatography, then crystallization, then drying) are possible. Examples include adding the chromatography resin directly to the fermentor or direct crystallization without chromatography.

Some types of products require special handling. Examples of these are the production of β-lactams (e.g., penicillins), steroids, and cytotoxins. Due to the nature of these products and the risks of carryover from batch to batch, they may be manufactured in dedicated facilities, with specialized safety and handling considerations. Marine microbes requiring salt in the medium is another special case. Salt, containing chloride ions, is very corrosive to stainless steel. Most fermentors and downstream processing equipment is made of 316 stainless steel. As a result of these complexities, some processing facilities will not conduct these fermentations.

XIV. SCALE-UP TO MANUFACTURING

Planning for scale-up to manufacturing biological products should begin as early in product development as possible. Prethinking the integration of technology platforms involved in preparation of a biological product can significantly accelerate process development for manufacture, scale-up, and demonstration of efficient, reliable, and robust production. Though the phases of product and process development seem sequential and independent, strategic integration will reduce the risk of failure due to process issues and will reduced overall costs and speed the introduction of an effective and safe product.

Some of the underlying sciences and technologies described earlier in this chapter have evolved to technology platforms that are recognized for their efficiency and reliability. A technology platform is a repeatable component of manufacturing that aims to reduce overall costs of development of a new entity, while increasing confidence that the product will meet its quality metrics and be reliably available within the required cost parameters. It is often a system of components whose performance, scalability, and reliability are known from previous use and validation. Examples of technology platforms include

- a host organism (e.g., microbial or mammalian cell) and a matched vector (e.g., plasmid, virus) for expression of a recombinant protein,
- specific defined media (including its preparation, sterilization, transport, feeding regimes, and impact on downstream purification),
- an inoculum train designed to reduce variability during scale-up to the manufacturing bioreactor (e.g., the optimized inoculum train described in the sect. "Reducing Variability and Throughput Time in Inoculum Development"), and
- a system of unit operations used to isolate an active metabolite from a fungal fermentation (e.g., cross-flow filtration to remove mycelia, followed by adsorption of a soluble active metabolite from the filtrate and elution of the metabolite from the adsorbant).

Technology platforms describe aggregated and integrated systems that give reproducible, scaleable performance. Technology platforms are broadly evident in the manufacture of small-molecular-weight biological molecules such as antibiotics and many of the inhibitors or activators of metabolism. The guides to fermentation and cell culture presented earlier in this chapter define examples of established technology platforms that optimize host biochemistry for small-molecule synthesis or protein expression. Technology platforms developed for small molecules often apply directly to manufacture of large molecules. For example, the unit operations designed for isolation and purification of small molecules may be reconfigured and optimized to reliably yield high-purity large molecules. Though each distinct macromolecule will have unique physical and chemical properties, if members of a family of macromolecules differ only slightly, such as monoclonal antibodies, it may be possible to link technology platforms to create generic manufacturing capabilities. Technology platforms utilized for large-scale production of monoclonal antibodies have become so flexible and reliable that they are industry standards utilized by all of the manufacturers of these recombinant macromolecules (57). In general, the larger and more complex the biological molecule [e.g., proteins, viruslike particles (VLPs) for presentation of a vaccine antigen], the more important it is to utilize proven technology platforms in achieving quality, performance, and licensing goals at full scale, in the shortest possible time. Integration of upstream and downstream manufacturing with choices made during product development can streamline connection of technology platforms to achieve best-in-class performance.

The section below addresses a philosophy for developing processes that support both early- and late-phase manufacturing needs. Though the example that is developed relates to a macromolecule (a "biologic"), the logic applies equally well to small molecules. The example below whose references illustrate these concepts for a complex molecule is production of a protein used as an antigen in a vaccine for an infectious virus.

XV. STRATEGIES FOR PROCESS DEVELOPMENT AND SCALE-UP OF BIOLOGICAL PRODUCTS

Product development begins in earnest once a new biological candidate is chosen and the initial proof of concept is completed. The next phases of development require larger amounts of material for study of factors that influence activity, preclinical testing, and provision of materials to support characterization and development of analytics. This is also the time for transition from purely laboratory processes to those that can support preclinical scale-up. Conventional approaches often neglect the long-term requirements for manufacture in favor of rapid preparation of the product for preclinical and clinical study; but small investments in prethinking manufacturing can still serve this function and yield a large payback later.

Conventional optimization of genetics for control of small-molecule production is undertaken to achieve reproducible kinetics of synthesis, overcome undesired or excessive regulation of product biosysthesis, and achieve genetic stability. These topics have been described earlier in the section "Regulation of Microbial Metabolism and Product Formation" and also apply to large molecular weight molecules. Where the product is a protein or protein derivative, it may be advantageous to move the genetics to a recombinant host platform that already has properties developed for reliable scale-up. It may also be necessary to identify a protein scaffold that will enhance biological activity of the protein or facilitate its recovery from upstream processing and purification (58–61). Optimization of the host, natural or recombinant, and its growth conditions should move forward at this point with defined media, if possible, and well-developed optimization strategies as outlined earlier in this chapter. The parameters described in the section on isolation and purification of biological products should be guides for defining the initial isolation of the product. A goal of not more than five to seven steps to final purity should be the target for scale-up from this point forward (Table 16). Typically isolation and purification processes for biologics follow the guidelines developed earlier in this chapter. These include filtration to isolate the initial product in either the fermentation or the cell culture broth, or in the cell mass, followed by release of the product in the cell mass and adsorption or extraction of the active component. Chromatography often can provide full purification to the final API bulk, but crystallization, which can be a powerful purification step for lower molecular weight products, may also be useful for some proteins (61).

XVI. BIOANALYTICS

Development of analytic methods during these early development stages is critically important, as they will establish the characterization of the biologically active product and form the basis for in-process control of the final manufacturing process. The role of measurement is central to robust process control, since one cannot control a step, transition, or process that cannot be measured effectively. A strategy that matches well with the end goal of licensure of a new product evaluates the important attributes of the final product and then follows those molecular characteristics back through the process to the earliest stages of fermentation or cell culture. In this way, the critical quality attributes (CQAs) become the bases of the critical process parameters (CPPs) for step-to-step control of the processes (62). The more complex the biological molecule, the more demanding the characterization required to support licensure of the product and linkage of the CQAs to the CPPs. For example, potency (defined by an in vitro or in vivo assay) and physical form (e.g., crystal size and form) may be sufficient to specify activity and bioavailability of an inhibitor of cholesterol biosynthesis. However, a complex vaccine presented to the human immune system as a VLP may require a map of the key epitopes[a] to define activity and an understanding of VLP stability to assess bioavailability (63). Complex molecules present difficult challenges to the efforts to fully characterize their important properties. However, careful characterization of the molecular parameters that define potency, safety, and efficacy will support efficient licensing of the changes in scale, manufacturing processes, or process relocation that will be inevitable during the life cycle of a biological product.

XVII. PRODUCTION OF A RECOMBINANT VACCINE IN *SACCHAROMYCES CEREVISIAE*

Vaccines are substances that stimulate the body's immune response, with the goal of preventing or controlling an infection or an undesirable metabolic event. They present an antigenic component that defines the specificity of the induced immune response. Other attributes of vaccine-induced immunity, such as the kinetics of the immune response, the longevity of the response (in terms of evidence of continued immunogenicity and protection), and even the specific type of immune response, may depend on formulation of the vaccine and its delivery to antigen-processing cells in the immune system cascade. Safety and efficacy are the universal arbiters of decisions that aim to establish vaccine quality (e.g., identity, potency, purity, immunologic response, protection and longevity, and vaccine stability) and manufacturability (e.g., scale-up, process robustness and reliability, worker and environmental safety, cost, the rates at which a manufacturing process can be developed, and the rates at which it can provide vaccine).

XVIII. TRIGGERING IMMUNE RESPONSE

Single, simple components of disease-causing agents seldom elicit an adequate immune response by themselves. Successful subunit vaccines are often designed to present the antigen, a subunit of the infectious organism, in particulate form (e.g., live or inactivated recombinant microbial cells or virus vectors, self-assembled mimics of cell or virion structure) or as subunits conjugated with other macromolecules that enhance immunogenicity (e.g., polysaccharide-protein conjugates). *Subunit vaccines* are those created from components of disease-causing organisms or their recombinant DNA analogs. Their goal is to maintain immunologic response and establish protection with reduced side effects and an increased safety margin over whole-organism vaccines. An example of a complex, successful subunit vaccine is the hepatitis B surface antigen (HBsAg) produced during hepatitis B infection in humans. Chronic hepatitis B infection and resultant liver disease may lead to formation of incomplete viral particles comprising the primary surface antigen of the virus self-assembled into 22 nm particles containing lipids and carbohydrate from the host. These particles (64,65) circulate in the blood of infected patients but are not infectious in their own right. During the late 1970s, Merck & Co., Inc., developed a manufacturing process for a subunit vaccine based on isolation of self-assembled surface antigen particles from infectious human blood plasma. The manufacturing process was complex, requiring full containment of materials, aseptic processing, and multistep inactivation of blood-borne microbial and viral pathogens. The vaccine, adsorbed to alum, was licensed in the United States in 1981.

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[a] The site on the surface of an antigen molecule to which an antibody attaches itself.

The world's first *recombinant subunit vaccine* was created by Merck Sharp and Dohme (Merck & Co., Inc., in the United States) to replace the product based on self-assembled surface antigen particles from infectious human blood plasma and was licensed in the United States in 1986. The recombinant vaccine was produced by inserting a plasmid containing the gene for HBsAg into baker's yeast (*Saccharomyces cerevisiae*). The recombinant yeast cells produce HBsAg, which self-assembles into the classical 22-nm particle, trapping yeast lipids and a small amount of yeast protein during assembly within the cell. The cells are harvested and broken open. The surface antigen particles are purified to more than 95% HBsAg protein homogeneity with a final protein content per dose of 5 to 40 micrograms/mL of sterile suspension. The product may contain yeast-derived proteins up to 5% of the final product and yeast-derived lipid but less than 10 micrograms of yeast DNA. This vaccine represented a significant improvement in the margin of safety. It could not result in hepatitis B viral infection or other human viral disease because no potentially infectious viral DNA or complete viral particles are produced in the recombinant system. The recombinant HBsAg is adsorbed to aluminum hydroxide (aluminum hydroxyphosphate sulfate), which acts as an adjuvant. Recombinant hepatitis B vaccine is produced by Merck (Recombivax HB) and GlaxoSmithKline (GSK) Pharmaceuticals (Engerix-B) in the United States.

Over time, the fermentation process for Recombivax HB manufacture in *S. cerevisiae* was dramatically improved. Though efficient complex media were developed (66,67) to support production, a chemically defined medium was eventually developed and used in production (34). Defined media for production of recombinant proteins in yeast (68) and other cells (69) have now become the industry norm. The *S. cerevisiae* platform for production of recombinant proteins has proven successful and is the basis for commercial production of the human papillomavirus (HPV) vaccine, Gardasil (70). Another example of the successful use of manufacturing platforms for complex molecules is the cell culture platform and standardized isolation and purification for monoclonal antibodies (57).

XIX. ESTIMATES OF CAPITAL AND OPERATING COSTS FOR MANUFACTURE FROM FERMENTATION OR CELL CULTURE

Example capital and operating costs of conventional fermentation, cell culture, and support activities are estimated below from the authors' experience supporting commercial production of API. The facilities assume fixed installations of final-stage fermentors or cell culture bioreactors with an inoculum development train of two bioreactors for each final vessel.

A. Facility Capital Costs

A small-scale integrated manufacturing and development facility for production of two to five products per year is hypothesized as a basis for estimating size, equipment, and staff. The development laboratories for this capability, including isolation and purification, might be accommodated in a 9000-sq ft facility. This facility could support scale-up in a small pilot plant included in the design parameters. The overall facility could be designed to support either cell culture or fermentation, housing a maximum of 75 staff. Capital cost for the laboratory space is estimated at $11 million (in 2008 U.S. dollars) based on construction costs of $1200 per sq ft.

A manufacturing fermentation suite, designed for a single product, utilizing an inoculum development train leading to a single 10,000 L production vessel could cost approximately $65 million based on actual small business cases. This plant would utilize fixed-tank technology with Clean-In-Place (CIP) and Sterilize-In-Place (SIP) automation. Expansion of the basis to support multiple products, with two separate trains of identical fermentors, is estimated at approximately $100 million, leading to a per-suite cost estimate for conventional plant design of approximately $48 million per suite. Costs for facilities with smaller capacities would clearly be lower. However, the cost basis for smaller capacity does not significantly drop until vessel sizes drop below the 1000 L scale, where skid-mounted processing units and disposable (single-use) technology (71,72) become feasible. This facility assumes multiproduct use across the operating year and modest requirements for purification. More sophisticated requirements for purification could drive the capital cost to 125% of the base case.

A single-suite facility to support cell culture would utilize a single 1500 L bioreactor and inoculum train to produce annual requirements for a protein vaccine. The cost for this hypothetical facility, in 2008 dollars, is $63 million. It would utilize disposable technology in most areas except the bioreactor and anticipates minimum purification requirements that might be appropriate for isolation of a VLP as a vaccine. An upper bound of 150% of the base case should accommodate more sophisticated requirements for purification.

Note the costs in this section apply to aqueous-based protein separation and that solvent-based processing will have higher downstream processing costs due to the need for specialized solvent-rated explosion-proof facilities.

B. Operating Costs

Operating costs, in US dollars, are estimated separately for a facility that carries out both Development and Manufacturing.

Development: An annual operating cost, excluding materials, for the process development laboratory could be approximately $13 million, based on a staff of 65 at a fully loaded annual cost of $200,000 per employee. The laboratories would be able to service up to five separate projects through scale-up in a small pilot plant. Facility and administrative costs are estimated at 18% of total capital investment, or $2.4 million. A total annual base operating value of $15.4 million per development laboratory is estimated for this hypothetical case.

Manufacturing: The fermentation production suite would be capable of making one batch of product per week. Operating cost estimates include all support functions. The estimated annual operating costs, based on operating staff (excluding materials), are:

- Manufacturing: 35 persons × $225,000 per person = $7.88 million
- Technical operations support: 5 persons × $190,000 = $0.95 million
- Quality control: 21 persons × $170,000 = $3.57 million
- Quality assurance/validation/document control: 21 persons × $160,000 = $3.36 million
- Administration/warehousing/maintenance: 19 staff × $150,000 = $2.85 million

The total is $18.7 million for operating costs, excluding ongoing capital costs for replaceable equipment and annual maintenance. Similar operating costs could be assumed for a cell culture facility. Costs do not account for raw materials and consumable durables (media, special buffers, resins, membranes, etc.) for each batch, since those costs are highly process and product specific.

All costs are in 2008 dollars, based on the index for Q4 of 2008, and assume annual productivity based on fermentation yields of up to 50 g/L of small molecules and cell culture yields of 10 g/L for recombinant proteins.

XX. CONTRACT MANUFACTURERS FOR API FROM FERMENTATION OR CELL CULTURE

Rapid expansion of the biotechnology and biopharmaceutical industries over the past several decades has led to many capable contract process development organizations (CDOs) and contract manufacturing organizations (CMOs) serving needs in fermentation, cell culture, biological product isolation and purification, and formulation and filling of biologically active APIs. The current trend of the CMO industry for biopharmaceutical products (including vaccines and monoclonal antibodies) indicates continued expansion in capacity to meet the demand from the private sector. In 2007 the biopharmaceutical CMO market increased by 14%, and the trend is expected to continue or expand over the long term (73). Demand for CMO cell culture technology continues to expand due to the fact that many newer biopharmaceutical drug products require molecular expression in mammalian/animal cell systems to establish optimum biological activity of recombinant proteins through post-translational processing (e.g., folding, glycosylation) or to support replication of viral vectors for vaccines. The contract sector for recombinant proteins expressed in microbial systems is less active in expansion but is still expected to grow over the next decade.

Technology platforms for cell culture, fermentation, and purification are beginning to standardize manufacturing process design and performance, leading to predictable costs for development and manufacture. A particularly good example of this is found in the manufacture of monoclonal antibodies (57). Large and small companies in the biopharmaceutical arena are expanding their use of CMOs to accelerate product introduction, while delaying capital investment decisions until product futures and economic conditions become more certain.

The development of single-use systems (disposable technologies) has created new opportunities to reduce operational lead times and overall operational costs. The biopharmaceutical industry and the CMO sector are utilizing these tools to support rapid preparation of early materials, reduce costs, and streamline technical support. Whether these are used as bioreactor systems [such as the wave bioreactor (74)] or as components in purification of recombinant proteins (75) or in support functions (such as media bags), there is potential to accelerate process development and early-stage manufacturing for some applications. Single-use systems for cell culture can generally maintain optimal growth conditions for cells and viral propagation, but such systems may limit performance of high-yield microbial processes that have higher oxygen transfer requirements. Large-scale, conventional bioreactors at CMOs are generally preferred for manufacture of biologics from bacterial fermentations.

Recent analyses suggest that over the next five years, biopharmaceutical contract manufacturing capacity for cell culture could expand by as much as 91%; and an increase of 33% is projected for microbial fermentation. CMO capacity expansion is greater than that projected for the integrated biotechnology industry (76). Capacity has transitioned from a period of relative undersupply to one of moderate oversupply. CMOs and users of CMOs have experienced stable to modest cost increases for large-molecule CDO/CMO services, but the outlook for the next few years is uncertain (2).

The large existing pipeline of products in the biotechnology and pharmaceutical industries continues to drive capacity utilization. Some of the CMOs are currently contracting manufacturing suite time 12 to 24 months in advance. Worldwide economic recession appeared in 2008 and may have delayed some planned expansion of CDO and CMO capacity, leading to a need to carefully plan access to CMO capability. The cost to manufacture a product at a CMO is approximately twice that needed for internal manufacture in a company's own dedicated facilities. At an appropriate cost premium of two, manufacture at CMOs versus internal manufacture is attractive if it frees internal capacity to develop new products.

XXI. CONTRACT DEVELOPMENT ORGANIZATIONS AND CONTRACT MANUFACTURING ORGANIZATIONS FOR FERMENTATION AND CELL CULTURE BIOLOGICAL PRODUCTS

There are literally hundreds of CDOs and CMOs across the world that offer a variety of services. Several organizations maintain databases of these important capabilities, for example, Genetic Engineering News (http://www.gendatabaseonline.com), Contract Pharma (http://www.contractpharma.com/csd/category/Fermentation), and the National Biotech Register (http://www.biotech-register.com/biotech-directory/CONZ.cfm). Some companies specialize in matching specific needs to CDOs and CMOs or in providing detailed analyses of options (e.g., High Tech Business Decisions, http://www.hightechdecisions.com/industry_bioman.html). The authors recommend a thorough evaluation of available information before choosing a particular CDO or CMO.

Some of the CDOs and CMOs that have proven, integrated capabilities for development and manufacture are listed in Table 17.

XXII. WHAT HAPPENS IF THE FERMENTATION OR CELL CULTURE DOES NOT PERFORM AS YOU EXPECT?

Problem solving in an industrial fermentation facility requires a different approach compared with that used in a laboratory environment. In an industrial regulatory environment you cannot make changes in an ad hoc manner, but the appropriate current Good Manufacturing Practice (cGMP) processes must be

TABLE 17 Authors' Selection of Representative CDO and CMO Vendors with Integrated Process Development Capability

Contract development and manufacturing organizations	Cell culture/ monoclonal antibody	Microbial/yeast fermentation	Primary location	Internet URL
Abbott Laboratories	X	X	Worldwide	http://www.abbottcontractmfg.com
Avecia Biologics		X	UK	http://www.avecia.com/biologics/default.htm
Baxter BioPharma Solutions	X		US	www.baxterbiopharmasolutions.com/contract_manufacturing/index.html
Biocon	X	X	India	http://www.biocon.com/biocon_services_contract.asp
Bioinvent	X		Sweden	http://www.bioinvent.com/
Boehringer Ingelheim GmbH	X	X	Germany	http://www.boehringer-ingelheim.com/corporate/ic/biopharmaceuticals/index.asp
Celltrion	X		S. Korea	http://www.celltrion.com/en/facility/facility_01.html
CMC Biologics A/S	X		Denmark	http://www.cmcbio.com/uk/services/cgmp-manufacturing/
Cook Pharmacia	X		US	http://www.cookpharmica.com/
Diosynth Biotechnology	X	X	US	http://www.diosynthbiotechnology.com/
GDS Technology		X	US	http://www.gdstechnology.com
Girindus AG/Solvay Organics		X	Germany	www.girindus.com
GlaxoSmithKline Biopharmaceuticals	X		US	http://www.gsk.com/biopharm
Human Genome Sciences	X		US	http://www.hgsi.com/manufacturing.html
IBA Biologics		X	Germany	http://www.iba-go.com/gmp/gmp_fr04.html
CMC ICOS Biologics	X	X	US	http://www.cmcbio.com/uk/about-us/
LG Life Sciences		X	S. Korea	http://lgls.com
Lonza	X	X	US	http://www.lonza.com
Sandoz	X	X	Austria	http://www.sandoz.com
Sanofi Aventis	X	X	Worldwide	http://en.sanofi-aventis.com/Default.aspx?s=manufacturer

Abbreviations: CDO, contract process development organization; CMO, contract manufacturing organization.
Source: For a comprehensive list see the databases of CMOs listed in the text.

followed. Another issue is the scale of the fermentation. You cannot do a large number of large-scale experiments to exactly replicate the factory conditions. Large plants are difficult to scale down exactly; not every variable will be kept constant on scale-down. A problem-solving methodology is presented below in the context of a fermentation facility. This methodology could be applied to the manufacture of any API but may simplify resolution of the challenging and complex issues associated with living systems.

The first step in such a situation is to form an investigation team whose mandate is to find the cause and prevent the reoccurrence of the problem. The composition of the investigation team is critical. Diversity in the team members' skills and expertise is vital. The team should include members with a broad range of skills and experience:

- A diversity of knowledge base and experience (some experts on problems, others not); fresh eyes are invaluable.
- Tacit knowledge (operators who know the plant).
- Some logical thinkers and some intuitive thinkers.
- The majority who are insiders and some outsiders. Independent members are important so that they can ask/say what they want. If the problem is significant someone outside the company can usefully be brought in to fill this role.

This team should function under the following rules:

- Have a stated mandate from the top and a project sponsor.
- Have an attitude of mutual respect and trust at all times, that is, a no-blame culture.
- Challenge vigorously.
- Acknowledge that no questions or statements are silly.
- Acknowledge that no one has a monopoly on the truth.
- Rotate the "devil's advocate" hat.
- Start with a wide investigation and narrow down.
- Be on time to meetings, and do the homework between meetings.
- Have wide powers to co-opt resources and people.
- Observe the process in the plant.
- Form specialist subcommittees.

Everyone in the company will be seeking progress reports and updates as the problem is solved. It is thus important to set a communications policy, for example, issue an e-mail status report at 5:00 p.m. every evening until the problem is solved.

A variety of tools or techniques can then be used to diagnose the problem.

- Tool 1: Sequence of events analysis. This is the best place to start and involves making a timeline of exactly what happened from the opening of master cell banks through the end of the failed fermentation. Listing the observations and symptoms provides a useful reference for the investigation team. It also enables comparison with similar datasets from previous successful fermentations. This analysis may reveal that critical pieces of data are not available, and options such as commissioning extra biochemical analyses on archival samples may be instigated.

TABLE 18 An Example of a Satellite Fermentation Subsample Set

Subsample experiment number	Sterilization	Inoculated at	Other variable changed	Effect tested at different scales
1	Large scale	Large scale	None	Control
2	Large scale	Small scale	None	Inoculum condition
3	Small scale	Small scale	None	Sterilization intensity
4	Large scale	Large scale	Medium composition	Medium composition
5	Large scale	Large scale	Operating condition, e.g., agitation or feeding regime	Operating conditions

- Tool 2: Satellite fermentations. These are extremely useful experiments in diagnosing large-scale problems. Satellite fermentations involve starting up the large-scale fermentation, taking subsamples at various points during the large-scale fermentation, and using these samples to run small-scale laboratory fermentations. These small-scale fermentations are run in parallel with the large-scale fermentation. This has the great advantage of being able to run a laboratory fermentation under nearly the same conditions as the large-scale fermentation. A typical satellite set of samples is shown in Table 18.
- Tool 3: Independent calculations and checking. Often a range of calculations are required to conduct the fermentation. These calculations may be of medium concentration when making up media, CER to control fermentation feeds, or the glucose feed rates to determine pump settings. It is useful to have someone independently check these calculations. Another good place to check is medium components. Ensure that the medium components actually used reflect what was intended. Identity checks on medium components and investigating raw material specifications can be very valuable. Another aspect to consider is the accumulation of undesired components in any recycle streams. In repeated batch fermentations (where the fermentor is continually almost emptied, with the remaining material being the inoculum for the next fermentation) there is a possibility for an undesirable product to accumulate. Another example might be the accumulation of an undesirable component in recycled solvents used to extract the fermentation broth.
- Tool 4: Thought experiments. It is sometimes useful to conduct thought experiments, which can suggest lines of enquiry, for example, considering answers to these questions.
  - What assumptions are we making?
  - How confident are we that the assumptions are true?
  - What would be the outcome if the assumptions were not true?
  - Which variable changes would duplicate the failure noted?
  - What was the first part of the fermentation, in which a deviation from normal was noticed?
  - Which variables can be definitely thought not to cause the issue?
  - Was the contaminant a waterborne organism?
  - What subsystems, for example, medium, sterilization, etc., should be focused on?

- Tool 5: Fault tree analysis. This involves forming a tree of all variables. Each major variable is broken down into further branches. The technique then looks at each branch, one at a time, and works out what the effect of changing the variable is, and following an investigation, a branch may be eliminated. For fermentation situations one fault tree may be
  - process and project specific variables,
  - services supplied, for example, steam, water, and electricity,
  - raw materials and other supplies,
  - data analysis or calculations and benchmarking against best practices,
  - standard operating procedures, and
  - physical design of the fermentor and associated equipment.
- Tool 6: Root cause failure analysis. This tool consists of asking *why* five times in a row. An example might be as follows:
  - Why did a contamination occur? The steam temperature was too low.
  - Why was the steam temperature low? There was water in the steam line.
  - Why was there water in the steam line? There was not enough pipe insulation (pipe lagging).
  - Why was there not enough pipe insulation? Because unplanned maintenance was in progress.
  - Why did the unplanned maintenance occur? Due to a steam leak related to another building.
  - Root cause: no control of interconnected systems

  The concept is that you solve the root cause to make the problem go away rather than simply addressing one of the higher-level symptoms. Addressing a higher-level symptom may mean the problem can reoccur.
- Tool 7: Failure mode analysis. This is a key tool in scale-up trials. It looks at how the fermentation fails. Was it a complete failure in which case no product is formed, or is it a proportional failure in which product titer is inversely proportional to scale. This gives a clue as to what the causative variable is. An example of a proportional failure is shown in Table 19.

If the fermentation failure is proportional, then look for variables that change their value in the same proportional fashion. If the failure is catastrophic, that is, no product is formed, then look for variables that change in a step-change fashion. The OTR may change inversely proportional to scale, while a change in medium component is a step-change variable, for example, the switch from laboratory chemical to industrial source on scale-up (Fig. 7).

The general paradigm of science should be followed, that is, form a hypothesis and gather data to prove or disprove the hypothesis. Early in the investigation it is often possible to have many different hypotheses active. It may be useful to have one group to argue one side of a hypothesis and another group

TABLE 19 An Example of a Proportional-Type Failure from Vinegar Fermentation

Scale of fermentation (L)	Product titer (%)
0.15	100
1.5	74
8	24
200	24

the opposite. When solved, communicate the cause accurately, recommend remedies, celebrate, and recognize the combined contribution of the team.

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15 Supply Management

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I. INTRODUCTION TO SUPPLY MANAGEMENT

An introduction to supply management can fill an entire textbook. The Institute for Supply Management (ISM) defines supply management as

> the identification, acquisition, access, positioning and management of resources and related capabilities the organization needs or potentially needs to attain its strategic objectives. The various components of supply management include disposition/investment recovery, distribution, inventory control, logistics, manufacturing supervision, materials management, packaging, product/service development, purchasing/procurement, quality, receiving, strategic sourcing, transportation/traffic/shipping and warehousing. (1) The purpose of this chapter is to introduce the most important aspects of supply management and, for each topic, to address the unique issues of the pharmaceutical industry. References are provided for those who want more detailed information about supply management in general and specific areas, in particular such as materials requirements planning.

Table 1 is a materials management matrix. It shows that a primary objective of marketing is to increase customer service of manufacturing to decrease operating expenses and of finance to decrease inventory. It also shows that as marketing tries to increase customer service, there is a tendency for operating expenses and inventory to increase contrary to the objectives of manufacturing and finance. Likewise, as manufacturing tries to decrease operating expenses, there is a tendency for customer service to decrease and inventory to increase. As finance tries to decrease inventory, there is a tendency for customer service to decrease and operating expenses to increase.

Therefore, there is a need to balance conflicting objectives. Materials management requires that conflicting objectives be balanced. The best approach to materials management (and to most aspects of life) is a balanced approach.

II. PRODUCTION PLANNING

The objective of production planning is to coordinate the use of a company's resources (materials, processes, equipment, and labor) to make the right goods at the right quality, at the right time, at the right (lowest total) cost.

The right quality is key in the pharmaceutical industry. Equipment utilized may be dedicated to a single product or be multipurpose. The multipurpose equipment requires thorough cleanout between different products. This cleanout and turnaround time between different products can be significant. A balance must be made between longer production runs (fewer cleanouts) and generally higher inventory and between shorter production runs (more cleanouts) and generally lower inventory.

TABLE 1 Materials Management Matrix

	Customer service	Operating expenses	Inventory
Marketing	*Increase*	Increase	Increase
Manufacturing	Decrease	*Decrease*	Increase
Finance	Decrease	Increase	*Decrease*

In the pharmaceutical industry, sometimes it makes more sense to have several dedicated lines, rather than one multipurpose line to avoid the cost of cleanouts and turnaround.

Production planning is made more challenging in the pharmaceutical industry with the introduction of new products. Trying to forecast the amount and timing for new products is made more difficult because of the need for pharmaceutical products to be approved by the Food and Drug Administration (FDA) before the products are allowed to be sold.

Pharmaceutical companies usually have to provide capacity for the new product before the new product is approved. Sometimes this initial production capacity may be outsourced to a custom manufacturer. In fact, outsourcing has become more important to the pharmaceutical industry, as pharmaceutical companies focus internal resources on developing new products and take advantage of the manufacturing capacity of external sources for both initial and long-term production capacities.

III. INVENTORY MANAGEMENT

Nowhere is a balanced approach more important than in inventory management.

I still remember the advice given to me by my manager when I first began purchasing materials for manufacturing. My manager explained that inventories should be kept as low as possible. My manager further explained that if inventories were found to be too high, I would probably be given a "slap on the hand." But my manager warned that if inventories should ever drop so low that the manufacturing operation was interrupted or a plant shut down, then I would probably lose my job. This advice made it clear to me which way I should err—the manufacturing operation was never shut down because of lack of production materials.

What is unique about the pharmaceutical industry is that the finished product is a product that can literally mean the difference between life and death for a patient in need of a life-saving drug. To run out of such a product could be deadly. Another reason why inventories might be maintained at higher levels in the pharmaceutical industry compared to other industries is that the pharmaceutical industry has historically been more profitable than many other industries. If a sale is lost because of lack of inventory, the opportunity cost is significant. The cost of the finished good is relatively small compared to the selling price of the pharmaceutical product.

It is interesting to note that even the US government kept inventory of pharmaceutical products, such as morphine, in its strategic warehouses to be prepared in the event of war or other situations where these important products might be needed.

The three primary categories of inventory to be managed are raw materials, work in process (WIP), and finished goods.

When materials are received to be used in the manufacture of a pharmaceutical product, an inspection (and possible testing) is usually necessary before the materials are accepted. Materials may be stored in a separate "quarantined" area until they are released and approved for use. The use of certified suppliers has allowed some materials to be received and accepted without additional inspection or testing. The certified supplier may provide a "certificate of analysis" documenting that the material meets the required specifications. Certified suppliers are usually audited to ensure that they meet the requirements for certification of the customer.

IV. PURCHASING/SUPPLY MANAGEMENT

Purchasing, procurement, supply management, and supply chain management are some of the names that are used to describe a function that continues to grow in value to organizations in general and pharmaceutical companies in particular.

Purchasing involves obtaining the right material (or services), at the right quality in the right quantities, at the right time, from the right source, at the right price.

Again the right quality is significant to the pharmaceutical industry. The supplier must understand the good manufacturing practices (GMPs). Supplier selection is critical. Supplier certification is important to many pharmaceutical companies. Suppliers must understand the importance of meeting specifications and controlling their processes to consistently meet specifications. They must notify the pharmaceutical company of any process changes.

Organizations generally spend a significant portion of their sales dollar in the purchase of materials and supplies, and an even greater share when services and capital are included. A small reduction in purchase cost may have the same impact on profit as a much larger increase in sales. This tremendous potential to increase profits has caused many organizations to focus more attention on the importance of purchasing and supply management. Purchasing and supply management professionals are adding value to their organizations through strategic cost reduction.

Some of the cost reduction strategies that have been used include the following.

A. Supplier Consolidation

Organizations are reducing the number of suppliers that they do business with. Reducing the number of suppliers for a particular commodity increases leverage. You become a more important customer to the supplier. The supplier can reduce the price based on the increased volume. Dealing with fewer suppliers allows for better supplier management. Purchasing and supply management professionals have limited time and can only effectively work with a limited number of suppliers. Consolidating suppliers allows more time to be spent with the most important suppliers.

B. Specifications

Specifications are important in cost reduction and management. You should purchase only what you need and not overspecify. As an example, when purchasing a chemical, the chemical may be offered in several grades with different levels of purity such as 98% or 99%. It is a waste to purchase the more expensive

99% purity chemical if the 98% purity chemical will meet the requirements to produce the desired product.

C. Standardization

Standardization helps reduce the number of different items purchased. For example, in the area of office supplies, instead of buying 10 different pens, purchase only 3 different pens. This increases the volume of the three selected pens and reduces the price and cost. For process equipment such as pumps, instead of purchasing 10 different pumps, purchase only 3 different pumps. This increases the volume of the three selected pumps and reduces the price and cost. But this also results in other benefits such as ease of operation and maintenance for the operators and mechanics who become more familiar with the three selected pumps. Another benefit is the reduction of spare parts. If you have 10 different models of pumps, you will need spare parts for all 10 models. If there are only three different models, you need to hold spares for only the three different models.

D. Competitive Bidding

Organizations can reduce costs through competitive bidding. This requires good specifications and a good scope of work. Purchasing will develop a request for proposal (RFP) that is sent to the preselected and qualified suppliers. Today many of these RFPs are sent over the Internet as electronic request for proposals (eRFPs). There is also an increased use of reverse auctions, where preselected and qualified suppliers will bid down the price of a specific commodity, with the business awarded to the qualified supplier with the lowest bid.

E. Negotiation

Negotiation is a key tool used to reduce cost. Good negotiation requires good preparation. Developing a negotiation brief before the negotiation is helpful in preparation for a successful negotiation. The negotiation brief will include information such as the history of the suppliers—current and potential and pricing. It will list the objectives of the negotiation, including what must be achieved and what would be nice to have. Negotiation is a skill that can be gained through education (courses such as Karrass) and experience. Successful negotiations are usually positive and are a win-win deal for both the supplier and the customer. It is usually possible to find a better deal for both parties.

F. Make Vs. Buy

Many pharmaceutical companies have chemical manufacturing capability. When a new product is being developed, these pharmaceutical companies have the option to manufacture the chemical or to purchase it from an outside chemical supplier. This allows the pharmaceutical company to do the make versus buy analysis and select the lowest cost alternative. When there is much external chemical manufacturing capacity, chemical suppliers are willing to "sharpen their pencils" and offer attractive pricing for chemicals.

G. Outsourcing

Organizations should decide what business they are in and what their core competency is. This is also true for pharmaceutical companies. Pharmaceutical companies may be involved with activities that are not core. As an example, facilities maintenance is an area that is not core and could be considered for outsourcing. To outsource successfully, it is important to develop the scope of the work that is to be outsourced. It is important to include all that is to be outsourced. If you miss something, the organization doing the outsourced work will be glad to add what you missed, but usually at a much higher price than if it had been included in the original scope of work. To make sure to include all that you want to outsource, it is important to have an outsourcing team with all the involved parties and especially those who are experts in what is to be outsourced. The outsourcing team should also include a representative from human resources, as some employees may be outsourced.

H. Policy

An organization's policy can have an impact on costs. A good example is a company policy on travel. Many companies have a policy on the class of air travel. A company may not allow and reimburse employees to travel by first class airfare. Business class travel may be allowed only for trips longer than a specified duration such as longer than eight hours. All other travel should normally be economy class. How the policy is set could help save the company significantly, but the policy must balance the needs of the traveling employee with the associated costs. If only economy class air travel is allowed, and employees are required to travel frequently on long flights such as between New York and Singapore, the employees may arrive tired and not be as productive as if they had been allowed to travel on business class.

I. Long-Term Agreements

Long-term agreements (3 years or longer) generally result in cost reduction. Suppliers are more willing to offer better pricing and invest more time to help with cost-saving ideas. The relationship between supplier and customer becomes more of an alliance relationship.

J. Global Sourcing

Globalization has affected all organizations and pharmaceutical companies in particular. Cost savings can be achieved by selecting the best suppliers in the world. Many of the chemicals and other materials that are used in the manufacture of pharmaceuticals are manufactured around the world in such countries as England, France, Germany, Switzerland, Italy, and Japan. In the future, more will be manufactured in emerging markets such as China and India. Also, the quality from these manufacturers can be excellent, but these sources must be carefully checked and managed. When there are multiple suppliers on more than one continent for a particular chemical or material, purchasing can take advantage of exchange rates to obtain better pricing and reduce total costs.

K. Reduce Freight Costs

Reducing freight costs of the incoming raw materials and supplies and the outgoing final products is an important way to reduce overall costs. There are opportunities for savings in all of the various modes of transportation, including truckload (TL), less than truckload (LTL), air, rail, ocean, and small package.

L. Reduce Lead Time

Reducing lead times is especially important to pharmaceutical companies when introducing new products. This allows organizations to obtain materials needed quickly from suppliers to meet unanticipated demand. Reduced lead times improve the time to market a new product.

M. Reduce Inventory

There is a need for balance when reducing inventory. Inventory should be kept low to reduce the dollars tied up in the cost of the inventory, the carrying costs of the inventory, and the cost of inventory that may go bad or expire. But inventory must be kept high enough to keep operations running smoothly without interruption. The inventory of final product should be kept high enough to make sure that every customer that needs the product can get it. For pharmaceutical products, this is especially important since these products could mean the difference between life and death for the patient.

N. Reduce Demand

Reducing demand is one of the best ways to reduce cost. If you are able to negotiate a 15% discount on an item, you can save 15%. But if you can find a way to eliminate the need to purchase that item, you have saved 100%—the full cost of the item. An example is a company that changed its travel policy to eliminate all business class air travel. Prior to the policy change, an employee could travel between New York and Singapore on business class. One particular traveler averaged four trips between New York and Singapore a year. After the policy change, this traveler saved much more than the difference between the price of the business and economy class fares, because the traveler made only two trips instead of four trips. For the two trips that were not taken, the traveler saved the company the full fare.

O. Reengineer Purchasing Process

Reengineering can start by documenting or mapping the current process. The next step is to identify and eliminate the non-value-adding or unnecessary steps. Most employees are being asked to do more with less, so it is important to examine all that is being done and eliminate the non-value-adding activities. Another approach to reengineering is to start with a blank piece of paper and list only the value-adding activities that should be done.

P. Automation/Information Technology

It is important to reengineer first so that the process that is automated is a good one. If you automate a "bad" process, you will just do the bad process quicker and consistently. Many companies have installed enterprise-wide information resource systems such as Oracle and SAP. These allow better information to be accessed for better decision making. It allows supply managers to see and better understand the spending—how much of what is being purchased by which suppliers. There are other systems that are being implemented to help direct the purchasing to the preferred suppliers to take advantage of the cost-saving agreements that have been negotiated. Many of these transactions are taking place or will take place in the future across the Internet.

Q. Transfer Best Practices

To improve performance, it is important to identify best practices and to implement them. If a best practice is found within an organization, it should be applied across the entire organization. Best practices should also be identified in other organizations and adopted (steal from the best). There are organizations such as the ISM and DCAT (formerly the Drug, Chemical & Allied Trades Association, now the Drug, Chemical & Associated Technologies Association) that offer seminars and programs to learn about these best practices. Within the ISM, there is the Pharmaceutical Forum and the Chemical Group, which along with DCAT offer educational and networking opportunities.

R. Energy Conservation

Energy conservation is and will continue to be an important way to reduce demand and costs.

S. Measurements

Measurements are needed to identify the opportunities for savings. Measurements are also used to improve internally and externally the performance of suppliers. It is important to measure what you want to manage.

Special note with regards to fermentation: The prices of some of the raw materials used in the fermentation process are impacted by the commodities market and soybeans in particular. It is important to monitor the commodities market, and at times, it may be useful to hedge the market to better control pricing.

V. DISTRIBUTION/TRANSPORTATION

Distribution involves getting the product to the customer at the right time. Channels are the particular paths in which the time goods move through distribution centers, wholesalers, and retailers.

Distribution requirements planning is a system approach that allows for distribution at minimum total cost.

Transportation involves the movement of raw materials from suppliers to production and finished goods to customers. It involves a variety of modes, including air, rail, motor (TL and LTL), and ocean freight.

Many pharmaceutical products must be maintained within specific temperature ranges. Some of these products must be shipped in refrigerated containers or trailers, commonly referred to as "reefers," at a premium price.

With many pharmaceutical companies having facilities in Puerto Rico (because of the past tax advantages), ocean shipments between the United States and Puerto Rico are common. Again many of these ocean shipments are made in refrigerated or temperature-controlled containers.

Even though air transportation is usually the most costly form of transportation, some pharmaceutical products are shipped by air for reasons of timing.

The pharmaceutical industry is a global industry. Suppliers are selected from the best suppliers in the world, and customers are located worldwide. Therefore, raw materials and final products are shipped all over the world, making transportation an important function within materials management.

VI. INFORMATION TECHNOLOGY

Information technology (IT) is an important area and will continue to become more important as time goes on. Many companies, including pharmaceutical companies, have been or are in the process of implementing enterprise information systems. For a global company, to be able to pull together information on a global basis is of great value. For example, to have quick access to the inventory of a raw material or a finished good on a global basis has allowed companies to reduce the amount of inventory. There is a substitution of information for inventory. The better the information available on inventory, the lower the levels of inventory required to satisfy customer requirements. The better the information available on what has been and is to be purchased from suppliers, the greater the negotiating leverage with those suppliers.

The particular system selected may not be as important as the need to understand if the system meets the requirements of the company. It is also better if the company implements an enterprise-wide system consistently across the entire company.

Some companies have selected information technology products with a "best of breed" approach. They selected the best purchasing system, the best accounts payable system, the best manufacturing resource planning system, etc. In theory this should yield the best overall system. In fact, several pharmaceutical companies that implemented this best of breed approach now realize some of the disadvantages of trying to interface the various systems. Each time any one of the individual systems is upgraded, there is the difficulty of upgrading the interface between the various systems.

Several of these companies now suggest that the best of breed approach may not be the best and that one overall system may be a better approach.

Many pharmaceutical companies are now using the Internet to communicate with and transact business with suppliers and customers. The use of the Internet by pharmaceutical companies will continue to grow.

VII. QUALITY MANAGEMENT

Quality management has become important to almost every industry but remains even more important to the pharmaceutical industry.

I have attempted to provide examples of the importance of quality in many of the previous sections of this chapter. Quality is so important to the pharmaceutical industry that a complete chapter of this text has been devoted to it.

Some of the areas to consider with regards to quality include current GMPs (cGMPs), ISO 9000 requirements, auditing, and validation.

The cGMPs provide the minimum guidelines for the production of drugs that are safe, pure, and effective. The FDA is charged with enforcing all provisions of the Food, Drug, and Cosmetic Act and regulations. The cGMPs are part of these regulations.

ISO 9000 is an international standard for quality management systems. The standards are not specific for any particular industry, but have been adopted and are used at least by some pharmaceutical companies. The ISO exists as a series of standards that covers design and development, production, installation and servicing, and inspection. The ISO requires that material identification and traceability be maintained, that suppliers are evaluated on a regular basis, and that training programs are established and documented.

Audits are conducted as a management tool for assessing the quality level of an operation. They are used to identify nonconformance, make corrective actions as needed, and prevent reoccurrence of potential problems that can adversely affect a product. Audits are conducted internally and externally. Supplier audits may be directed "for cause," such as a customer complaint, for change control, or for a product problem. Audits may be scheduled on a regular basis (e.g., every three years) for suppliers of key or critical materials.

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16 Equipment Maintenance and Reliability

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I. INTRODUCTION

The field of maintenance has changed considerably, perhaps more than any other business discipline over the past 50 years, and the pharmaceutical industry is also responding to these changes by addressing maintenance and reliability issues better to produce life-saving products, on time, on cost, on quality, and safely with respect for personnel, property, and the environment. Many leading pharmaceutical companies and biotechnology firms have been investing in developing asset care programs and manufacturing excellence strategies over the past 20 years to implement strategic plans for equipment maintenance and reliability.

For the pharmaceutical industry, maintenance is no longer a repair and restore function that is called upon to fix a malfunctioning asset or facility. There is a large, complicated code of federal regulations that cover many compliance requirements that impact the maintenance function in the pharmaceutical sites. Depending on the type of compliance factor involved, that is, electronic documentation, good manufacturing practices, safety, environmental emissions, fired equipment permits, mechanical integrity of equipment, fitness for service requirements, factory acceptance testing, etc., there are large volumes of data collection, documentation, and record-keeping requirements, including evidence of service, audit, and compliance, that fall within the scope of maintenance and reliability departments. Regulations from governmental and local agencies, such as the United States we have the Food and Drug Administration (FDA), the Occupational Safety and Health Administration (OSHA), the Environmental Protection Agency (EPA), etc., that greatly impact the maintenance function in pharmaceutical sites. While we will briefly discuss the maintenance aspects of these issues, a detailed review of compliance-related aspects may be found in other chapters within this book.

Our consulting experience in the pharmaceutical industry shows that by and large, the primary focus of the maintenance department is on performing day-to-day reactive maintenance and necessary preventive maintenance (PM) programs. The reliability departments (often referred to as asset excellence, asset care, asset improvement, etc.) are primarily in the early stages of formation or operating at a basic beginner level. The organizational structure of the reliability departments in many instances is not very clear. In several situations, it is created as a subset of the maintenance or the operations department. In some cases, the asset care function is merged under a corporate business support group.

We have observed that there is a much stronger focus at the senior management level on new product launches, meeting of production schedules, and product channeling, marketing, and distribution compared with initiatives on preserving existing assets and equipment reliability and extending the useful life of the assets. As the economic landscape for the pharmaceutical industry changes in the United States and Western Europe with a severe squeeze on the profit, margins along with an avalanche of competition from low-cost generic

Maintenance Basics
Good Documentation Practices
Complete Asset Registry
Condition Monitoring
Operator Performed Maintenance
Reliability Engineering
Design for Reliability
Maintenance Risk Management

FIGURE 1 Reliability fundamentals program (1).

drug manufacturers and political pressure to keep drug prices low, it is our opinion that senior management focus will need to shift quickly so that existing, installed assets and sites are operated reliably and efficiently with a reduced total cost of ownership. Equipment maintenance and reliability will get increasing attention in the coming years as management will realize the economics of reliable operations; stable, consistent asset performance; and improved mechanical integrity of the assets.

In this chapter, we have outlined a basic nine-point "Reliability Fundamentals Program" that is best suited for the pharmaceutical industry, especially where the asset variety is large and complex—process equipment, cryogenic equipment, facilities, packaging lines, batch sites, continuous and semi-continuous sites, etc., at a single site (Fig. 1). The level of investment and strategic fit for a reliability program depends on the industry, code of regulations for compliance, economic climate, and equipment code requirements for safe operations. While underlying reliability issues may be the same, the reliability programs should be tailored for the applicable industry, since the risk profiles are different, that is, airline, nuclear, petrochemical, mining, etc.

The basic program we have outlined is based on what we have seen as driving factors for the pharmaceutical industry. It is a composite sketch of what many corporations have been attempting to implement over the past 20 years. The implementation success map is mixed. Some corporations are basically still in the evaluation mode, trying to see if there is a business justification for doing so, while in other instances there are good success stories to report. However, by and large, in most pharmaceutical companies we have observed that there are pockets of excellence; that is, some of the program elements have been applied, adopted, and implemented successfully, whereas the other remaining elements are still in various stages of implementation.

A "Reliability Fundamentals Program" should have the following eight elements (Fig. 1):

We will discuss each of the eight elements in this chapter along with a multiyear, strategic plan for implementation of the program. It is important that the program implementation have the appropriate commitment at the leadership level and be targeted at a wide cross section of the site population. These reliability programs are highly cross-functional, multiyear implementation efforts with focus groups working in parallel on different elements toward the same reliability and maintenance goals.

To drive this kind of program across a large, global enterprise, there must be a strategic plan developed that will provide the guiding principles for the program.

II. STRATEGIC PLAN (2)

Before embarking on the implementation of the reliability program, it is highly recommended that the leadership formulate a strategic plan addressing the following issues:

A. *Vision:* Where will we be in three to five years?
B. *Mission:* How will the vision be reached?
C. *Goals and objectives:* How will we know when we get there and what it was worth?
D. *Philosophy:* What will our maintenance and reliability culture be after the program is implemented?
E. *Organizational structure:* How will our structure change during the journey?
F. *Rewards:* How will all personnel be recognized for their efforts and achievements?
G. *Training:* What training will be required to reach our destination?
H. *Maintenance role:* How will the role of the maintenance department change during the next three to five years? Will the maintenance department exist as a separate function in five years? Will it be the maintenance and reliability department? Will it be the reliability department?
I. *Technology:* What role will technology play? An example is interfacing process control computers to a Computerized Maintenance Management System (CMMS) for integrated condition monitoring, which will lead to a sound predictive maintenance program.
J. *Capital strategy:* What sort of capital spending will be required to reach our goals?
K. *Workforce strategy:* How will hourly personnel be involved? Will we have to negotiate significant change?
L. *Customer strategy:* How will our customers be involved in our journey? What will our achievements mean to our customers?
M. *Vendor strategy:* What will change in our relationships with our vendors of services and materials, and how will the benefits be measured?

III. RELIABILITY FUNDAMENTALS PROGRAM

A. Maintenance Basics

There are a number of issues that must be addressed in the maintenance basics arena in order for a pharmaceutical site to achieve excellence in maintenance. Without the maintenance basics in place, there is not much of a foundation to build upon. It is absolutely essential that these fundamentals be properly implemented and established before the other elements are launched. The maintenance basics consist of the following: performance measures, work order controls, preventive/predictive maintenance, spare parts management, operations/maintenance relations, training/continuing education, and the CMMS.

1. Performance Measures

The first step in establishing an effective maintenance basics program is to identify and establish performance measures. Most experienced managers have learned that "you get what you measure." Successful pharmaceutical sites develop and implement a series of supportive key performance measures to track and manage improvement of maintenance/reliability. Examples are mean time between failure, maintenance cost per unit of output, percent planned and scheduled maintenance, PM tasks completed, expense maintenance cost as a percentage of replacement asset value, etc. These indicators must be available to all levels of an organization and should be used to maximize individual and group contributions.

2. Work Order Controls

Most cost-effective sites have a systematized approach to identifying, prioritizing, planning, scheduling, executing, and recording routine maintenance. This would include site shutdowns.

3. Preventive/Predictive Maintenance

Cost-effective sites have an equipment criticality-ranking scheme and use reliability-centered maintenance techniques to determine the equipment that requires PM. They use a combination of equipment manufacturers' recommendations, experience, and available PM databases to validate or modify existing PMs and to create new PM schedules where necessary; then they faithfully execute their PM programs.

4. Spare Parts (Stores) Management

Getting the right spare part to the right place on time is an important step in effective maintenance materials management. Cost-effective pharmaceutical sites employ proper systems, procedures, and practices relating to the procurement and management of maintenance spare parts. Size of spare parts inventory and other procurement costs are often excessive in pharmaceutical sites because of the ongoing campaigns to produce new products with ever-changing site equipment. Vigilance is required to manage this situation. Vendor stocking programs (VSPs), consignment inventory, electronic data interchange (EDI), bar coding, cycle counting, and other techniques should be used to reduce inventory levels.

5. Operations/Maintenance Relations

Solid customer/supplier relationships or, even better, partnerships between operations and maintenance are essential in the pursuit of maintenance excellence. The enemy is not inside the site walls.

6. Training/Continuing Education

An organization must inventory skills training requirements and provide training. It also must focus on consistent implementation of roles and responsibilities with all levels of the organization to ensure that the right things get done correctly, on time, and safely. A special subset of roles and responsibilities is multiskill maintenance. Pacesetter sites have a flexible work crew with a broad base of skills, supported by specialists.

7. CMMS

The final factor in maintenance basics, the CMMS, ties all the issues together. Actually it institutionalizes the behaviors required to achieve maintenance excellence. Typically, it has a work control module, an inventory module, and a purchasing module and ties to financial systems, payables, the general ledger, etc. For large-enterprise implementations, the CMMS is referred to as the Enterprise Asset Management (EAM) system. Today, there are several "on-condition" systems such as Ivara's EXP® that enhance a CMMS. A key issue with a CMMS or on-condition system is that it can, if used properly, provide the "evidence of service" required by FDA regulations. The CMMS is also an essential element of the "Good Documentation Practices" protocol, often referred to as "GDP."

B. Good Documentation Practices (3)

There are various types of documentation that reside within a corporation, each having a specific purpose, intent, and application. In the maintenance arena, there are various types of documentation that are often confusing, and end users have a problem understanding the subtle differences between them. There are various document types: guidelines, job plans, procedures, policies, strategy papers, work orders, standards, technical directives, etc (Fig. 2).

While each corporation establishes its own GDP protocol and there is no universal definition of what GDP should look like, we have provided a brief generic explanation on what should be the main intent of establishing GDP within a pharmaceutical organization for a maintenance department. A document pyramid is the best form of documenting information and maintenance work processes. Each document should have its own repository or storing place (Figs. 3 and 4).

Maintenance vision and strategy documents papers should be visible at the widest possible level with a broad distribution network, that is, Web site, notice boards, newsletters, etc. These should be brief and easy to comprehend with clear, simple statements that reflect the leadership goals for equipment

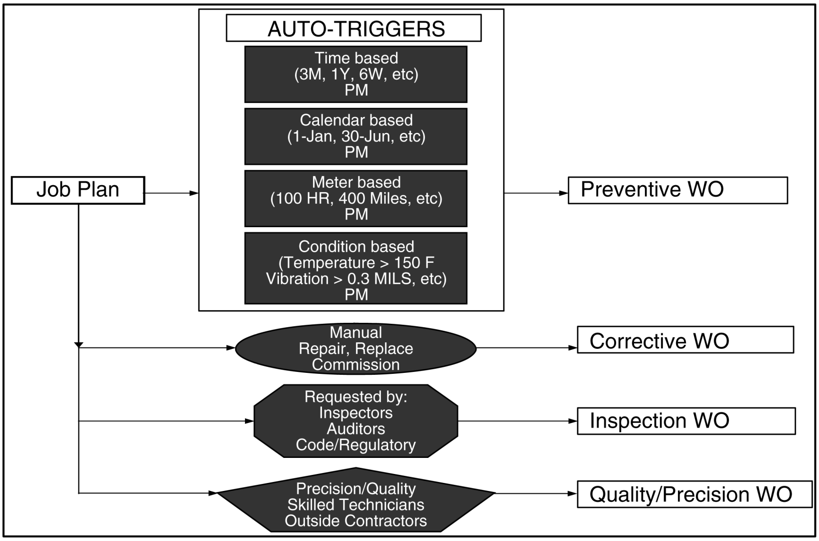
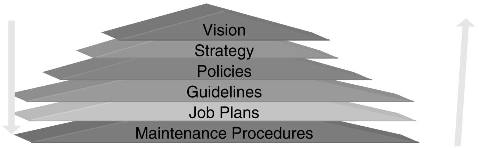

AUTO-TRIGGERS
Time based (3M, 1Y, 6W, etc) PM
Calendar based (1-Jan, 30-Jun, etc) PM
Meter based (100 HR, 400 Miles, etc) PM
Condition based (Temperature > 150 F Vibration > 0.3 MILS, etc) PM
Job Plan
Preventive WO
Manual Repair, Replace Commission
Corrective WO
Requested by: Inspectors Auditors Code/Regulatory
Inspection WO
Precision/Quality Skilled Technicians Outside Contractors
Quality/Precision WO

FIGURE 2 Job plan conversion to a work order (4).

Document Pyramid

- Job plans and procedures are the means for company direction to be administered at the micro level (shop floor)



Each document occupies a certain place in the hierarchy

FIGURE 3 Document pyramid structure (4).

Component Failures	**Severity**	**Probability** (absent planned Maintenance)	**Critical**	**Maintenance**
Fails to Close Remotely	Mission	Med	Yes	• Measure spring tensions, clearances and alignment @ 36 months • Lubricate whenever disassembled • Visually Inspect/Test/Operate @ 12 months
Fails to Open Remotely	Marginal	Med	Yes	• Measure spring tensions, clearances and alignment @ 36 months • Lubricate whenever disassembled • Visually Inspect/Test/Operate @ 12 months
Fails to Remain Closed	Mission	Med	Yes	• Measure spring tensions, clearances and alignment @ 36 months • Lubricate whenever disassembled • Visually Inspect/Test/Operate @ 12 months
Fails to Trip on an Overcurrent Condition	Catastr-ophic	Med	Yes	• Measure spring tensions, clearances and alignment @ 36 months • Lubricate whenever disassembled • Visually Inspect/Test/Operate @ 12 months • Calibrate @ 12 months

Component Failures	**Severity**	**Probability** (absent planned Maintenance)	**Critical**	**Maintenance**
External Leakage (cooled seal water)	Minor	Low	No	None– Restoration Deleted as Result of RCM Analysis
External Leakage (cooling Elec & Aux Fresh Water)	Minor	Low	No	None– Restoration Deleted as Result of RCM Analysis
Internal Leakage	Minor	Low	No	None– Restoration Deleted as Result of RCM Analysis
Reduced Capacity/ Flow rate	Minor	Low	No	None– Restoration Deleted as Result of RCM Analysis

FIGURE 4 Simplified failure modes study—typical model (5).

maintenance and reliability—for example, zero mechanical integrity leaks, 100% PM compliance, no maintenance schedule breakers, etc.

Maintenance policies should be developed that outline how the strategy and vision goals will be achieved. Typical maintenance work policies could be "Weekly Condition-Monitoring Routes," "PM Planning," "Equipment Design Policies," etc. Policies are documents that are mainly of a governance type so that the organization's directives for maintenance work and documentation processes are enforced.

Guidelines are essentially working-level documents that reflect the details contained in a maintenance policy. For example, there could be several "equipment design guidelines" referenced to an equipment design policy. Guidelines could reference existing codes and standards, such as American Petroleum Institute (API), American Society of Mechanical Engineers (ASME), American National Standards Institute (ANSI), Society of Automotive Engineers (SAE), 21CFR (Code of Federal Regulations) Part 210, Part 211, etc.

Job plans are essentially step-by-step job instructions for the mechanic or technician to follow on a maintenance work order. A CMMS is the repository for all equipment and maintenance job plans. Job plans must be short, concise, checklist-type instructions that an experienced mechanic should be able to perform and document. Job plans enhance craft productivity and are critical to asset reliability and maintenance programs in a corporation. They are extremely useful for sustaining best practices and increasingly critical as more regulatory issues, insurance, and code-related inspections are becoming the norm. Most important, they serve as a final checklist in the field for the mechanic/technician performing the work.

The main problem existing in many corporations is that job plans are written by many individuals, each having a distinct style and concept of what should be the content of a job plan. Some writers elaborate extensively and provide convoluted, confusing statements instead of clear, precise job tasks. Instead they compose narratives or full-length procedures. This is an important distinction that many corporations confuse—job plans versus maintenance procedures.

Maintenance procedures are detailed recipe-type work instructions that could be referenced to a specific work instruction. For example, a job instruction could be "isolate pump motor." The corresponding maintenance procedure should provide detailed instructions on the way to perform the specific maintenance task of isolating the pump motor, tools to use, safety precautions to be observed, protective gear to be worn, job prerequisites, minimum training to be completed prior to performing the task, etc.

At the very minimum, there should be six clearly defined document types for the maintenance organization. A world-class maintenance organization should have good maintenance procedures, job plans, guidelines, policies, and well-documented strategies.

C. Asset Registry (5)

Asset registry is a complete database of all assets within a site, organized in a well-defined hierarchy, with "parent-child" relationships. All assets, active or idled, must be registered in the database, which is usually the CMMS or EAM. For the registry to be considered complete, it is imperative that all types of assets and their information be contained in the database. We have provided a list of asset types that should be registered in the CMMS. Without a complete database, it is difficult for an organization to implement a world-class reliability program. In our experience, this is usually the most difficult element to implement in a reliability fundamentals program. In many corporations, it usually takes one or two full-time individuals to keep the asset registry up to date and complete. Every time a repair or maintenance is performed and an asset is replaced or moved, the asset registry must be updated to reflect an accurate asset inventory. An asset registry is viewed as "complete" only if all the following asset types and information are updated in the CMMS.

1. Mechanical assets: pumps, blowers, fans, compressors, mixers, agitators, screw feeders, injectors, etc.
2. Fixed/stationary assets: tanks, pumps, reactors, block valves, exchangers, columns, coolers, freezers, etc.
3. Electrical assets: transformers, switch gear, motor control centers, motors, panels, junction boxes, etc.
4. Hydraulic assets: jacks, hoists, lifts, elevators, escalators, platforms, etc.
5. Instrumentation: transmitters, sensors, analyzers, relays, control valves, switches, indicators, etc.
6. Facility assets: heating, ventilating, and air-conditioning (HVAC), laboratory equipment, boilers, water treatment systems, controllers, etc.
7. Buildings and administration areas: cafeteria equipment, fire systems, security systems, scanners, etc.
8. Support equipment: cranes, hoists, trailers, vehicles, trucks, security gates, card scanners, cameras, etc.
9. Garbage and treatment systems: sewers, treatment ponds, holdup areas, remote analyzers, etc.

Asset information is critical for the asset registry. We recommend at least the following asset information to be entered in the asset registry.

1. Name plate information
2. Purchasing specifications
3. Location of the asset
4. Associated storeroom for parts
5. List of all spare parts
6. List of assemblies (if the asset is an assembly of several assets)
7. Criticality rank of the asset
8. Asset classification (asset type, subtype, category, etc.)
9. Asset status indicator (idle, active, retired, etc.)
10. Asset group (functional equipment grouping, e.g., an instrument on a pumping station assigned to the group "pump station")

D. Condition Monitoring

There are three steps that a pharmaceutical site should take to implement an effective condition-monitoring program.

1. Identify Equipment

The first step in implementing a condition-monitoring program is to determine what equipment will be monitored. It will be critical equipment and generally is about 10% of the total equipment. All manufacturing and environmental control equipment should be evaluated.

2. Select Technologies

The next step is to choose the technologies that will be employed. Typically, well-maintained and reliable pharmaceutical sites employ vibration monitoring, thermography, radiography, infrared, particulate count, detailed motor analyses, and environmental monitoring. The key to a successful condition-monitoring program is to select the appropriate technology on the particular asset at the right condition-monitoring frequency.

3. Implementation

Routes and timing are established, people are trained, and the program is implemented. Readings are taken, analyses are performed, and recommendations for action are provided to maintenance, engineering, and operations. A strict condition-monitoring discipline will lead a site to a successful predictive maintenance environment, where people at all levels of a site will be able to visualize the resultant equipment "saves."

There are many condition-monitoring systems that can extend the functionality of a CMMS. Examples are Bentley Nevada®, GE system 1®, Ivara EXP®, Prognost®, etc. Integration of these software tools to the corporate EAM/CMMS can greatly shrink the response time for maintenance to take appropriate corrective action on detection of a "condition." If the installed equipment base is large (generally 10,000 or more assets), condition-monitoring system integration with a CMMS is easily justifiable. For smaller sites, a careful evaluation needs to be made to determine the economic justification.

E. Operator-Performed Maintenance

Many corporations are heavily investing in operator-performed maintenance routines. The benefits are obvious; that is, an operator takes care of his or her equipment as the first level of basic care and only calls maintenance if the level of malfunction is above a certain threshold. The principle is also termed as "autonomous maintenance" and has been very successful in Japanese auto companies in improving overall equipment reliability and lowering the cost of maintenance.

Toyota is famous for the total productive maintenance (TPM) process implemented at sites worldwide. The intent is to increase operators' ownership of their equipment and its reliability. The process encompasses many of the activities of TPM. Four key areas of focus on implementation of an operator-driven reliability program are:

1. Selection of the operator-performed duties, generally minor maintenance tasks such as lubrication, cleaning, observations, refilling of machinery fluids, labeling, etc.
2. Improving adherence to equipment procedures (start-up, operation, and shutdowns). A lot of machine setup tasks, alignments, start-up checklists, and shutdown checklists are gradually being transferred to operations from maintenance. Maintenance should be purely viewed as a second level of equipment care support.
3. Improving communication, coordination, and problem solving between production and maintenance. With operator-performed maintenance programs, the level of communication increases three to four times compared to environments where traditional maintenance is performed.

4. Increasing operators' responsibilities in housekeeping, equipment inspection, and performance of minor maintenance.

A final thought: In North America, only the power generation sector of the heavy industry regularly employs the operator/maintainer concept. We recommend that the pharmaceutical industry explore this concept.

F. Reliability Engineering

Reliability engineering consists of the systematic application of time-honored engineering principles and techniques throughout a product or process life cycle and is thus an essential component of a good product life cycle management (PLM) program or a Good Manufacturing Practice (GMP) program as it is typically referred to in the pharmaceutical world. The goal of reliability engineering is to evaluate the inherent reliability of equipment or a process and pinpoint potential areas for reliability improvement. Realistically, all failures cannot be eliminated from a design, so another goal of reliability engineering is to identify the most likely failures and then identify appropriate actions to mitigate the effects of those failures.

Application of reliability principles to an evaluation of a process involves a number of analyses and techniques. The different reliability analyses are all related and examine the reliability of the overall system from different perspectives to determine possible problems and assist in analyzing corrections and improvements.

Reliability engineering can be done by a variety of engineers, including reliability engineers, quality engineers, test engineers, systems engineers, and design engineers. In highly evolved teams, all key engineers are aware of their responsibilities in regard to reliability and work together to help improve the product.

The reliability engineering activity should be an ongoing process in the pharmaceutical industry, as the manufacturing process consists of many asset types and process phases. The goal always needs to be to identify potential reliability problems as early as possible in the process life cycle.

In our view, the area of reliability engineering finds the pharmaceutical industry well behind the refining/petrochemical industry. A great deal of "catch-up" will be required for the typical pharmaceutical site in terms of engineering skills, sustainability of the reliability engineering process, and management's understanding of the economic value this effort brings to the business. In the past 10 years, we have seen efforts made by the pharmaceutical industry to recognize these various tools and adopt them in its day-to-day manufacturing and maintenance environments. Some of the formally recognized reliability tools are as follows.

1. Reliability-Centered Maintenance

Reliability-centered maintenance (RCM) provides an engineering risk-based technique for managing equipment performance. The method takes the large, highly nonintuitive problem of identifying high-risk failure modes and divides it into many small, easily solved problems to design a risk-based maintenance plan.

While there are many flavors of RCM that are adopted in the industry today, the main intent and goal is to develop an appropriate maintenance strategy for an asset to preserve the system function. The key steps in an RCM study are as follows:

- Determine system functions and functional failures.
- Identify equipment functional failures and failure modes.
- Determine potential local, system, and transportation failure effects.
- Determine severity based on possible failure consequences.
- Determine failure probability (absent planned maintenance).
- Identify critical failures—based on probability and severity.
- Prescribe maintenance tasks targeted at failure modes that are:
  - Applicable (work to prevent failure)
  - Effective (pay for themselves)
- Compare/revise existing maintenance plans by asset class.
- Monitor feedback data over time for plan refinement.

Many vendors offer software tools and databases to support the administration and facilitation of RCM studies. We have seen that the pharmaceutical industry has adopted several RCM approaches, and there are no recommendations as such for the industry for any particular RCM technique.

2. Failure Mode Study (6)

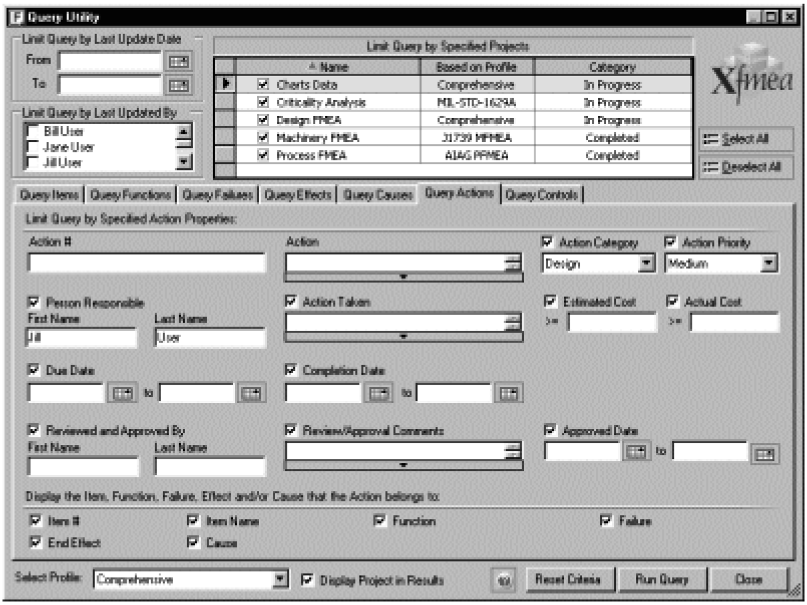
In this approach, potential failure modes of critical equipment are ranked according to their risk (probability × consequence). Typically 80% of the equipment's total risk is due to 30% of its failure modes. The failure mode study allows management to allocate scarce resources (labor, materials, and equipment) on a cost-effective basis to attack high-risk potential failures. The failure mode and effects analysis (FMEA) can be performed using a simple spreadsheet-based approach and can also be used using advanced software that allows libraries of system functional failures to be logged and analyzed. Figure 5 shows an example of how this type of analysis is performed.

3. Root Cause Analysis of Recurring Failures (6)

In most pharmaceutical sites, over one-half of the work orders completed are unnecessary maintenance. Sites need to establish a systematic approach of recognizing/analyzing recurring failures and determining/correcting the root causes. This eliminates unnecessary downtime and reduces maintenance expenditures for labor and materials. Also there is reduced risk of safety and environmental incidents.

4. Maintainability Review

This three-pronged approach to improve equipment reliability is based on failure analysis to identify root causes, testing of equipment immediately after repair to ensure quality work was performed, and performance analysis of equipment to determine equipment efficiency rates and replacement intervals. This methodology uses predictive technologies. The unique feature in this approach is to ensure that the asset is well positioned to carry out online condition monitoring or repair maintenance with the least level of intrusive approach.


Query Utility
Limit Query by Last Update Date
From
To
Limit Query by Last Updated By
☐ Bill User
☐ Jane User
☐ Jill User
Limit Query by Specified Projects
Xfmea
Select All
Deselect All
Query Items
Query Functions
Query Failures
Query Effects
Query Causes
Query Actions
Query Controls
Reset Criteria
Run Query
Close

Name	Based on Profile	Category
☑ Charts Data	Comprehensive	In Progress
☑ Criticality Analysis	MIL-STD-1629A	In Progress
☑ Design FMEA	Comprehensive	In Progress
☑ Machinery FMEA	J1739 MFMEA	Completed
☑ Process FMEA	AIAG PFMEA	Completed

Limit Query by Specified Action Properties:

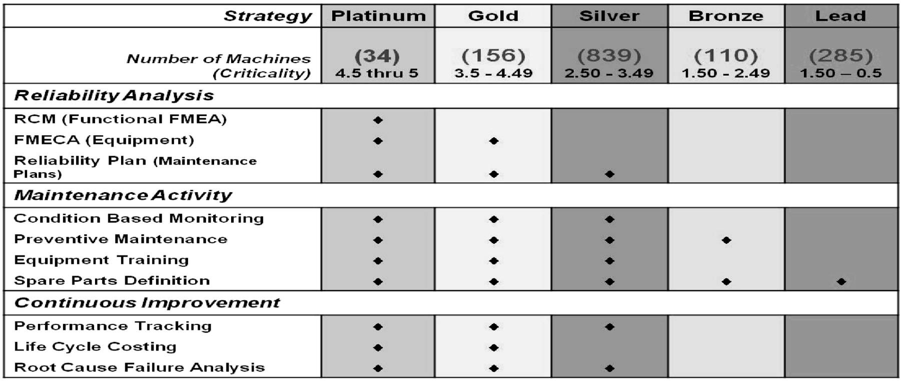
Action #
Action
☑ Action Category: Design
☑ Action Priority: Medium
☑ Person Responsible — First Name: Jill — Last Name: User
☑ Action Taken
☑ Estimated Cost >=
☑ Actual Cost >=
☑ Due Date to
☑ Completion Date to
☑ Reviewed and Approved By — First Name — Last Name
☑ Review/Approval Comments
☑ Approved Date to

Display the Item, Function, Failure, Effect and/or Cause that the Action belongs to:

☑ Item # ☑ Item Name ☑ Function ☑ Failure
☑ End Effect ☑ Cause

Select Profile: Comprehensive ☑ Display Project in Results

FIGURE 5 Advanced FMEA software with built-in library functions. *Abbreviation*: FMEA, failure mode and effects analysis (7).



Strategy	Platinum	Gold	Silver	Bronze	Lead
Number of Machines (Criticality)	(34) 4.5 thru 5	(156) 3.5 - 4.49	(839) 2.50 - 3.49	(110) 1.50 - 2.49	(285) 1.50 – 0.5
Reliability Analysis					
RCM (Functional FMEA)	◆				
FMECA (Equipment)	◆	◆			
Reliability Plan (Maintenance Plans)	◆	◆	◆		
Maintenance Activity					
Condition Based Monitoring	◆	◆	◆		
Preventive Maintenance	◆	◆	◆	◆	
Equipment Training	◆	◆	◆		
Spare Parts Definition	◆	◆	◆	◆	◆
Continuous Improvement					
Performance Tracking	◆	◆	◆		
Life Cycle Costing	◆	◆			
Root Cause Failure Analysis	◆	◆	◆		

FIGURE 6 Illustration of physical asset reliability strategies (8).

5. *Equipment Standardization/Simplification*

A physical assets strategy is developed to focus on simplifying and standardizing equipment throughout a site. Successful implementation of the strategy reduces training and repair costs. This is particularly important in the ongoing "campaign" approach of the typical batch pharmaceutical site. Figure 6 shows how this approach has been applied at a leading pharmaceutical company where various strategy models have been developed and applied based on equipment criticalities.

6. Reliability Reporting

In this type of calculation, special training is offered to maintenance supervisors and workers to show them how to measure and track reliability for equipment in their areas. The focus is on building reliability indices for key equipment such as pumps, compressors, and motors. Assistance is provided on helping people establish overall equipment effectiveness (OEE) and mean time between repair (MTBR) measures for their areas. This method involves performing statistical calculations over a population of a certain asset type or class.

7. Concurrent Engineering

New engineering techniques are implemented to ensure that engineering projects are not developed in isolation. Cross-functional teams (engineering, production, maintenance, etc.) are involved in the design, installation, and testing of new equipment to ensure that reliability, maintainability, standardization, performance, and cost specifications for new equipment are met. It is also very important to coordinate engineering efforts at the corporate, site, and area levels. During a shutdown in a pharmaceutical site, we observed three different maintenance crews attempting to accomplish three distinctly different modifications to the same unit on the basis of instructions from three separate engineering functions within the company. Life cycle costing is an important engineering technique that has gained considerable attention within the pharmaceutical industry where engineering decisions and equipment selections are made on the basis of the total cost of ownership of the asset, including asset design, procurement, commissioning, operation, repair, and demolition. There are various spreadsheet-based models that are available for life cycle costing, depending on the asset and cash flow–modeling techniques [e.g., net present value (NPV), internal rate of return (IRR), earnings before interest and taxes (EBIT), etc.]

8. Bottleneck Study

Continuous flow manufacturing (CFM) techniques are used to identify manufacturing bottlenecks, especially those caused by inadequate reliability or maintenance practices. By prioritizing the most critical bottlenecks, appropriate resources can be applied to maximize production throughput.

There are many other reliability-based analyses that are quite advanced and require complex software for modeling and simulation that are beyond the scope of the reliability fundamentals program. We will simply list some of the reliability tools that have been applied in high-end reliability applications such as aerospace, refining, nuclear power generation, etc., but a detailed discussion is beyond the scope of this chapter.

Advanced tools that may be of interest to seasoned reliability professionals are:

- *Life data analysis* involving statistical modeling of the failure histories and prediction of cost-effective PM intervals and replacement strategies
- *Monte Carlo simulation* of asset performance cycles, including failures, PM, scheduled and unscheduled events, cluster shutdowns, partial malfunctions and degradations, etc.
- *RAM simulations* involving reliability, availability, and maintainability modeling of various scenarios and "what-if" events for a system or assembly of assets

- *Three-dimensional (3-D) modeling* involving generation of 3D imaging of equipment (generally of large vessels and piping), highlighting areas or sections where the risk of mechanical integrity leaks is high, that is, dead legs, low-point drains, corrosion points, moisture deposition surfaces, etc.
- *Risk-based inspection (RBI)* philosophies where inspection profiles are generated on the basis of a comprehensive risk model of an asset..

G. Design for Reliability

Design for reliability (DFR) is a design philosophy that must be committed at the highest level in an organization for all capital and engineering projects within the organization (9). It is an approach based on a simple principle that all engineering design decisions, asset selections, and process designs must be completed with a specific reliability and mission availability target. Typically this is done in the design phase by systematically analyzing every possible failure mode and developing mitigation measures either by redundancy, technology improvement, enhancement of the maintainability function, or installation of multiple standby units online.

DFR is not a new concept, but it has begun to receive a great deal of attention in recent years since the proliferation of Six Sigma, Lean Sigma, and Lean Manufacturing concepts in the pharmaceutical industry. DFR is adopted and deployed with a few modifications across different industries in a way that fits well with Six Sigma principles, since many of the statistical tools and techniques are the same for both.

In the project design life cycle, many decisions are made regarding engineering tolerances, excess capacity, sparing, redundancy, energy optimizations, etc. With the implementation of DFR, reliability becomes an important factor in all design decisions of a capital project. Specifically, DFR describes the entire set of tools that support product and process design (typically from early in the concept stage all the way through to commission of the capital project) to ensure that expectations for reliability are fully met. In other words, DFR is a systematic, streamlined, concurrent engineering program in which reliability engineering is weaved into the total development cycle. It relies on an array of reliability engineering tools along with a proper understanding of when and how and to use these tools throughout the design cycle.

As the pharmaceutical industry consolidates and streamlines its operations by shutting down excess capacity and focuses on improving the reliability of operating assets, engineering managers and reliability engineers have come to this realization that a more structured process for weaving reliability into the design phase itself is needed. It is much more expensive to carry out retrofits to improve reliability once the assets have already been commissioned. A wide range of DFR tools and techniques are deployed by practicing engineers to ensure that the design basis for the capital project includes considerations from reliability factors. Examples of the some of the tools used are:

- *Reliability modeling*: life data analysis, Weibull, system availability simulations (1)
- *Design of experiments (DOE)*: evaluating the optimal design from a reliability perspective

- *Design FMEA*: iterations of FMEA on various design options being considered to generate a library of all possible functional failure modes and their consequences
- *Reliability growth modeling*: a statistical framework of calculations to determine the improvement or growth in reliability throughout the design life cycle

H. Maintenance Risk Management (7)

Manufacturing excellence is achieved when the leadership focuses on driving reliability gains through a systematic, sustainable framework of initiatives, as described in this chapter. As the site's assets perform and operate reliably, the site's safety and environmental compliance record also improves, since there are less events of unforeseen downtime and reactive maintenance.

In the pharmaceutical industry, "risk" is a wide, broad term, since it applies to a whole range of issues from manufacturing, marketing, distribution, and product liabilities. In this chapter we focus on the risk factors in the maintenance sector only (7). Compliance is an increasing headache for maintenance and operation managers in a pharmaceutical site since the record-keeping and documentation requirements, as listed in 21 CFR Part 11, 21 CFR Part 210, and 21 CFR Part 211. In addition, OSHA requires all areas that are designated as process safety management (PSM) in the operating site should maintain compliance with the 14 PSM elements. These areas are subject to OSHA audits and citations.

Assets critical for "drug" manufacturing and identified as GMP have a separate list of requirements. All asset records, including insertions, changes, updates, deletions, and archiving pertaining to GMP assets, must be established in software that is "validated" from a functional, integration, and data integrity standpoint. In addition, all maintenance work entries must be logged and flagged with software that is 21 CFR Part 11 compliant, that is, electronic records and electronic signatures.

For GMP areas, all instrument calibrations, analyzer maintenance records, centrifuge speed test results, etc., require strenuous record keeping and documentation regarding how the instruments were tested, when they were tested, what the results were, who interpreted the results, how the results were validated, etc. Similarly equipment setups prior to a manufacturing campaign require extensive documentation.

SUMMARY

Excellence in the maintenance and reliability arenas is best achieved by pursuing a logical, methodical approach, such as we have outlined in this chapter (8). The pharmaceutical industry must move away from views such as "maintenance is a necessary evil" or "maintenance is an art" to a reasoned, empirical approach. The industry cannot afford to squander its heavy investment in research and development and its excellence in marketing by neglecting the maintenance and reliability function. As the economics of the pharmaceutical business changes, it is more and more imperative that equipment reliability and maintenance excellence will be powerful success drivers.

ACKNOWLEDGMENTS

We wish to thank our clients in the pharmaceutical industry with whom we have worked over the years to develop and fine-tune the overall map of the reliability fundamentals program.

The author would like to thank Raymond J. Oliverson for his assistance and support in writing this chapter.

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Printed in the United States of America

H100022

ISBN 978-143980336-3

90003

9 781439 803363

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www.informahealthcarebooks.com

52 Vanderbilt Avenue
New York, NY 10017

Telephone House
69-77 Paul Street
London EC2A 4LQ, UK